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Reason for report:

INDUSTRY UPDATE

HEALTHCARE

Is COVID Serology Antibody Testing Really Ready For The Big Reopening?

S&P 500 Health Care Index: **1,173.93**

Companies Highlighted:
ABT, BDX

• **Bottom Line: COVID-19 serology testing is emerging as a key pillar in reopening of the economy and will have significant implications on public health decisions for healthcare providers, employers, COVID therapeutics trials and the broader U.S. population.** Reopening hinges on a massive number of high quality serology or antibody tests launching in a short time-period, despite historically such tests taking years to decades for development and refinement (as in the case of HIV). Extremely high demands for such serology assays in the midst of FDA's very generous and approving EUA guidelines is risking the market being flooded by low performing assays that hold the potential to deliver inadequate results and misdirect public health efforts. FDA, CDC and regulatory response is still lacking standards for target and antibody levels - at a time when regulators have an obligation and a responsibility to establish those standards for diagnostic manufacturers to meet. Despite these critical challenges, we are seeing some early but promising signs as large test manufacturers step up to launch their serology assays - with most recent data from ABT (MP), which is likely followed by Roche, with DHR (Beckman), DIA-IT, BIO and Siemens (SIE-ETR) around the corner.

• **Reopening and economic outlook hinges on serology assays: high quality tests and massive volume ramp-up will be required.** In this note we detail the current state of serology tests for COVID-19, and the implications for public health and the economy. We also highlight early announcements and companies that are likely to benefit from the ramp with a focus on performance and availability to deliver on what appears to be a massive need as the population returns to work, convalescent plasma trials ramp, healthcare providers are routinely tested, and as employers test their workforce. We see that timelines will be rushed and performance compromises will be made in the near-term.

• **High performance and ability to scale will be rewarded; early data from ABT looks promising.** High performance and the ability to scale to millions of tests is critical. ABT recently announced promising data with the launch of its serology assay that delivers high sensitivity (100%) and high specificity (99.6%) 14 days after symptoms, with early independent work supporting performance. ABT plans to scale up 4M tests over the next week, and to 20M tests in June. Immunoassay manufacturers will likely see a tailwind from this serology testing ramp and testing algorithms involving both molecular and serology testing should start to emerge.

• **Regulatory efforts from FDA to standardize and set early guidelines are still lacking.** Lack of standards and guidelines is likely to create confusion as different manufacturers ramp up individual assays. Cross comparisons will be challenged. We lay out a number of recommendations to reduce friction and address primary concerns for the parties involved.

Serology Testing for COVID-19: Ready for Primetime or Another Testing Mess?

As the population emerges from COVID-19 peak, the need for serology or antibody testing is rapidly rising to identify individuals who have already developed antibodies to COVID-19 and can potentially safely return to work. Serology or blood-based antibody tests that look for immune response in the form of immunoglobulins (IgG, IgM, IgA) hold the most promise here. The base serology immunoglobulin assays are generally easy to develop but refining them to deliver high performance (high negative predictive value [NPV], positive predictive value [PPV]) could take years as it took 3 decades of refinement for the HIV serological assay to be perfected. With the global pandemic ongoing, and high priorities given to development of such assays, we believe the time to develop a high performing assay should be shorter still with continuous improvements to the assays as data on the biology, pathogenesis and epidemiology of SARS-CoV-2 emerges. These assays can also help identify individuals with antibodies to SARS-CoV-2, get patients enrolled into convalescent plasma trials and also help conduct population screening to identify the penetrance of COVID-19 in the population. Despite those being the key indications, the quality and scalability of these serology assays are going to be key considerations in an outbreak where rapid scalability, reliability, and high performance is desired.

As of now, despite having 70+ serology assays being announced, though not all submitted to FDA given lenient standards, (mostly lateral flow or strip based) and announcements from both Roche and ABT who are launching their COVID-19 IgG assays on their widely distributed immunoassay platforms, **we still don't have these assays independently validated to assess those that are high quality and ready to test the broader population**. If we assume that some U.S. states are expected to open in the next 2 weeks, one would be highly skeptical of reaching any meaningful impact from these assays in next 2-3 weeks for returning back to work scenario/indication.

FDA, CDC and regulatory response is still lacking standards for target and antibody levels - at a time when regulators have an obligation and a responsibility to establish those standards for diagnostic manufacturers to meet. We are seeing lagging response as the NCI (National Cancer Institute) just announced (on 4/14) that NCI's HPV vaccine and serology study laboratory will validate these assays to identify those that deliver high performance vs those that don't. This information is supposed to be coordinated with the NCI, FDA and the CDC but regulatory slips during the earlier response to COVID-19 in February and March raise doubts that FDA and CDC will manage to oversee and adjudicate the process appropriately. These efforts are being announced at a time when both European countries and UK are rejecting a number of lateral flow serology assays emerging from China.

Major Economic and Public Health Decisions Hinge on Serology Testing

Major economic and public health decisions hinge on serology testing with healthcare workers being the first in line to demand these tests today. Though the complete picture of the immune response and duration of protection remains unclear, there is a strong market need for such assays from healthcare providers to employers that would like to test their employees returning to work and ultimately the broader population. Both high quality data and the ability to rapidly ramp

up serology assays will give more certainty to reopening for the economy. Ultimately, we see the potential for the entire U.S. population to be tested with serology. If the immune protection is found to be limited, these assays also hold potential to be utilized annually driving long-term upside to diagnostics manufacturers involved.

Getting the Workforce Back to Work

Though ultimately the true benefit and the actual utility of such an assay will be more important in the second or third wave of the outbreak vs today, we still see that early versions ("ver 1.0") of the serology assays will see significant demand nonetheless in the current outbreak. Recent COVID-19 serology testing announcements from leading companies including Abbott (ABT), Roche, (ROG-SWX), Danaher (DHR), DiaSorin (DIA-IT), Siemens and others are likely to be most impactful. ABT's serology data is already looking promising, and we see both ABT and Roche appearing to be delivering the most comprehensive testing offerings from molecular to serology. Vaccines will continue to hold the final backstop to the pandemic, but until then, and even after the introduction of a potential vaccine, we see both molecular and serology testing to continue to become key pillars in the standard of care for COVID-19 and potentially all influenza like viral diseases.

Abbott's Early Data Look Promising; Multiple Independent Validations Key to Boosting Confidence

Early data from ABT's recent launch of its assay on the ARCHITECT immunoanalyzer system looks promising (100% sensitivity, 99.6% specificity) for the IgG antibody. IgG normally requires testing 14 days after the first symptoms show up. Early independent data is also looking in line with what ABT had released but further independent validation by NCI would be useful.

Abbott announced the launch of their third COVID-19 test – this time a serology assay vs prior two being RT-PCR and antigen based. This lab-based serology test is for IgG antibody detection and will be available on their ARCHITECT i1000SR and i2000SR instruments, of which there are over 2,000 currently in use in U.S. labs, that can run 100-200 tests per hour. Abbott expects to immediately ship 1M tests (last week), and 4M by the end of April (approx. 2-week period), with expectations of ramping to 20M tests in June and beyond**.** The test is expected to expand to IgM antibody detection in time.

In ABT's internal validation, which included 122 serum and plasm samples collected from 31 subjects who had previously tested positive for SARS-CoV-2 via PCR, and 1,070 serum and plasma samples from assumed negative subjects, which included 997 collected prior to September 2019, and 73 collected in 2020, after the outbreak started. Abbott's IgG assay achieved 100% sensitivity for those 14+ days post symptoms (positive agreement according to ABT) and 99.6% total specificity (negative agreement) with RT-PCR, with only four false positives from the 1,070 negative sample. In the package insert for the assay, Abbott broke the test performance on known positive patients into four buckets according to days post symptom onset and IgG response was strong after 14 days. This timing is not surprising in our view, given the nature of IgG antibodies being created later in the immune system's response to a virus.

This performance speaks to the true accuracy of the test, in our view. These tests are not designed or expected to be used earlier on in the diagnostic paradigm, but more so as a method to identify those that have recovered and have built immunity. Overall, we view these early results favorably, especially as they are from one of the major test developers that we believe can meaningfully scale production into the tens of millions a month relatively quickly.

We were also encouraged to hear of Abbott's intentions to release a lateral flow assay. While still in development, this assay will likely be scalable to millions of people within a short period of time, offering an easy access and quick result testing option directly at the point of care. **Independently, this data was also validated by Univ of Washington Virology lab on their ARCHITECT system over the last 4 days. The lab tested slightly more than 400 patient samples and obtained similar results.** The assay in their hand showed no cross-reactivity, negative samples were found to be negative, and of 14 patients that were detected to have COVID-19, 7 of them were found to be in the hospital with the rest having shown up earlier for COVID like symptoms.

Figure 1. Abbott IgG Antibody Assay Validation Performance

The results of both groups are presented in the following 2 tables.

Positive Agreement by Days Post-Symptom Onset

Days Post-Symptom Onset	n	Positive	Negative	PPA (95% CI)
< 3	5	0	5	0.00% (0.00, 52.18)
3 - 7	10	5	5	50.00% (18.71, 81.29)
8 - 13	34	31	3	91.18% (76.32, 98.14)
≥ 14	**73**	**73**	**0**	**100.00% (95.07, 100.00)**

Negative Agreement by Category

Category	n	Positive	Negative	NPA (95% CI)
Pre-COVID-19 Outbreak	997	4	993	99.60% (98.98, 99.89)
Other Respiratory Illness	73	0	73	100.00% (95.07, 100.00)
Total	**1070**	**4**	**1066**	**99.63% (99.05, 99.90)**

Source: Abbott

Figure 2. Assuming sensitivity of 100% and specificity of 99.63%, Abbott IgG Antibody should deliver high clinical PPV and NPV for COVID-19 antibodies if the early data were to hold

NPV and PPV Assuming 95% Sensitivity and Specificity						
Prevalence	1%	5%	10%	25%	50%	75%
NPV	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
PPV	73.2%	93.4%	96.8%	98.9%	99.6%	99.9%
Sensitivity	100%					
Specificity	99.63%					

Source: ABT, SVB Leerink

Serological Assays and the Indications For COVID-19

Serological or blood-based assays are designed to identify those individuals that have developed the antibodies (seropositive) for the pathogen (in this case SARS-CoV-2) after infection. These individuals are thus called seroconverted vs those that don't have the antibodies (seronegative). When comparing the current COVID-19 pandemic, the closest example of serological assay comes from 1980's crisis of HIV where a serological assay was developed and then refined over 30+ years. What took HIV serological assay 30+ years is hard to establish overnight for COVID-19, but given the magnitude of the crisis, we remain confident that today's "version 1.0" assays should have a place given the demand levels and are bound to improve over time in a rapid fashion as more data regarding the biology and pathology of COVID-19 emerges.

Four Indications Worth Noting

Based on our conversations with key KOLs, pathologists, and lab directors, we see 4 key indications for the serology assays. Each indication in our view comes with its own requirements, and challenges, including type of test (strip based or central lab), performance requirements, scalability and commercialization. Each indication has its own importance for global health and economic recovery and creates an opportunity for the larger instrument and diagnostic names to generate revenues and solidify their reputation.

(1) "Getting workforce back to work" Assay: With sky-rocketing unemployment levels, school closures and work from home requirements, an assay that helps identify those who have been exposed and developed immunity (seropositive) for the virus, is likely to carry immense value and be widely used. The COVID-19 Serology or antibody assay is being touted as "go back to work assay" or "all clear assay" among industry and the public. The assay in this indication is a key element for helping patients return to work to drive the economy to prior levels of output. As this test is expected to reach a broad population in the millions in the U.S. and the world, the best approach would be to use a lateral flow (strip or dip stick) based immunoassays, however such assays take years to perfect (as in the case of HIV). We see early antibody tests emerging in central lab or core labs and operating on immunoanalyzers and also providing antibody titer information.

(2) **Identifying recovered patients for convalescent plasma.** Convalescent plasma (CP) is an emerging treatment for COVID-19 that relies on transferrable immunity from individuals that have previously had significant disease and then recovered. The plasma fraction of blood transfers only the serum proteins, and therefore omits any cellular components of the response to the virus, but in other viral infections CP has proven useful in acute treatment. The early suggestions about the response to CP is quite positive, with the treatment offering a transitional option for patients with severe disease to prevent their progression to ventilation or death. One of the conditions for developing effective CP is to confirm the presence of antibodies, and ideally confirm that they are neutralizing antibodies and not non-neutralizing ones. Ideally an assay for these purposes would include quantitative measurement of antibody levels, to allow concentration of donor plasma from high titer donors, and to exclude low titer contributors from the pool. At this stage we don't know what the threshold for such donations should be, but it seems likely that such a threshold will be established in the near future. Please see our Biopharma Team's note (Link, 03/30/2020) highlighting two early studies on CP transfusion for COVID-19 treatment.

(3) **Population screening assay:** A population-based screening effort to determine penetration of the virus into the population. To truly understand the spread of the virus, population-based testing is required. While testing the entire population for exposure to the virus is unrealistic, large test groups (several thousands to millions) over time are likely to drive further understanding of the virus, and can provide key spread information that can have significant impact on the end outcome and response to the virus, such as the virus seroprevalence or reach into the population. Understanding the reach of the virus can help shape a more targeted and safe response to the pandemic.

(4) **Potential confirmation of vaccine efficacy in the longer term.** As most observers now know, there are more than 70 different vaccine development programs underway with at least 3 already in the clinic. Vaccine development timelines are aggressive, and not terribly definite, and all depend on showing immunity through surrogate markers. The surrogate markers are almost certainly antibody assays, most likely to the spike protein. Since all of the vaccines will generate different antibodies, they are likely to require different companion diagnostics. Since the vaccines will not have proven clinical protection at the time of introduction, and since the correlation of protection will be to just a handful of animal results, it is almost inevitable that antibody assays will be required to confirm a response. This is particularly likely to be true for the first populations eligible for vaccination, namely healthcare workers and first responders. These populations are likely to need to prove seroconversion before they return to the workplace after vaccination, and even in the general population, when vaccines are introduced, we expect confirmation of a response (with an antibody assay) to be required. This confirmation of response is the same standard that has been required for healthcare workers given Hepatitis B vaccines, and for other situations such as transplant patients, or those expecting to experience immunosuppression for other reasons.

Large Choice of Serology Assays; Questions Over Performance Are Being Raised

With recent announcements from Roche and Abbott, we are anticipating significant initial volume of serological assays. With expectations of Roche to ramp to 100M tests per month, and Abbott to 20M tests per month, testing capacity appears sufficient early on compared to initial hiccups in RT-PCR molecular testing for diagnosing patients. The early ramp in testing capacity has the potential to alleviate future backlog from compiling, given the serology portion of the testing algorithm is still being defined. We see continued upside to this total capacity as more large-scale test developers bring their assays to market, and ultimately, we believe that the majority of market will be dominated by a few select immunoassay manufacturers.

While expectations of the serology test ramp appear sufficient, questions are likely to remain on performance. In this note, we dive into KOL commentary on serology testing expectations and the history of serology testing in HIV over the past 30 years. Initial internal assay validations for lateral flow assays don't appear to be convincing and will required independent validation. That is exactly where we see NCI contributing over the next few weeks. We expect to watch the program closely and see if it leads to recommendations for certain assays over others. Furthermore, with current FDA leniency in the serology testing space, it has driven more skepticism among KOLs, who raise questions about purchasing assays from smaller developers over concern of scalability, while cautioning on artificially high performance numbers as a whole.

Early Use of Serology Testing Highlights Challenges with Adoption of Tests on Back of Limited Known Performance Metrics

Two newsworthy stories out of serology testing the past two weeks include full antibody screens for two communities; Fisher Island in Florida, and San Miguel County in Colorado. Collectively, these two efforts present a total testing opportunity of over 10k individuals. The Fisher Island tests are run by BioMedomics (lateral flow) while the San Miguel County tests use an ELISA approach by United Biomedical. While these tests are being used in broader populations, we believe questions still remain on the overall performance. The BioMedomics assay had shown 88.66% sensitivity and 90.63% specificity when tested with 397 blood samples from multiple hospitals and the CDC. On April 10, The University of Miami Health System at Fisher Island suggested that of the 1,500 people they had tested using the BioMedomics lateral flow test, positive rates ranged from 4% - 5%. Using the reported sensitivity and specificity numbers from BioMedomics, we calculate a ~33.2% PPV at 5% prevalence, suggesting a low probability of someone testing positive actually having the disease. These datasets stand in a complete contrast to what we have seen from ABT so far, pointing out challenges with lateral flow assays.

Figure 3.BioMedomics PPV and NPV Calculation

BioMedomics Lateral Flow NPV and PPV Assumption						
Prevalence	1%	5%	10%	25%	50%	75%
NPV	99.9%	99.3%	98.6%	96.0%	88.9%	72.7%
PPV	8.7%	33.2%	51.3%	75.9%	90.4%	96.6%
Sensitivity	88.66%					
Specificity	90.63%					

Source: BioMedomics, SVB Leerink

In San Miguel County, Colorado, test results are still incoming with the second wave of testing delayed. From March 19 through April 6, officials collected samples from ~5,500 of 8,200 residents for testing, however as of April 15, only 1,975 results have been received. Delays have been a result of compromised staff and access to supplies as a result of the pandemic, highlighting another overarching issue of effectively rolling out tests to millions other than just testing capacity. The County has provided few updates into test results to date with the experience, however announced on April 14th that 344 results were received (the first since March 31) with 3 positives and 5 "borderline persons". Previously, the County reported 986 test results including 8 positives, 23 indeterminates and 955 negatives, while 645 first responders saw 0 positives in the initial wave of testing. Collectively, inclusive of the "indeterminate" cases as presumed positives, the positivity rate is only ~2%. Of the initial phase of screening, there are still ~3,500 tests outstanding.

Figure 4.Collective San Miguel County, Colorado, Antibody Screening Results to Date (04/17/2020)

San Miguel County Test Results					
	Positive	Indeterm.	Negative	**Total**	Pos Rate.
Update 1	0	0	645	**645**	0.0%
Update 2	8	23	955	**986**	3.1%
Update 3	3	5	336	**344**	2.3%
Total	11	28	1,936	**1975**	2.0%

Note: Pos rate includes indeterminate results as presumptive positives

Source: San Miguel County, Colorado, SVB Leerink

Key Challenges and Focal Points for Serology Assays in COVID-19

Over the past few weeks we have researched this topic and spoke with multiple pathologist KOLs, lab directors, assay developers and management teams about the prospect of serology testing adoption**.** Beyond performance requirements, the feedback provide us with key points that must be considered for a serology-based assay:

- **A manufacturer's ability to scale.** With serology tests likely needed in tens of millions or more, the KOLs we have spoken to have suggested that a manufacturer's ability to scale is one of the biggest challenges they will face, highlighting that no lab director would buy test

kits from a manufacture if they had any doubts about receiving their full order or being able to re-order kits on a regular basis.

- **A more lenient FDA creating a market flood of un-validated tests.** Last week, the FDA announced that over 70 developers had notified the FDA that they have serology test kits available for use, though at this time only 4 tests have been approved. While the FDA's EUA guidelines allow tests to be marketed commercially prior to receiving emergency use approval, the flood of tests on the market has created a false expectation of "rapid diagnosis" that is accurate among the general public, and more complexity for those who are seeking to purchase serology assays.
- **Lateral flow (strip based) vs. central lab model.** Serology tests can be run as a lateral flow, strip-based assay, or in a central lab on an immunoanalyzer platform, both of which have advantages and disadvantages. A strip based test offers patients a rapid turnaround, getting a qualitative yes or no answer within minutes, suggesting the presence of the antibody, while a central lab model offers titer information, a more quantitative result highlighting the level of antibody response, though with a longer turnaround time (2-3 days) given the logistics involved and nature of running the assay on an instrument. While we expect the market to utilize both testing methods, the ultimate split remains to be seen, and is likely dependent on the overall performance of the assays and prevalence of the virus.

Based on our work, we reviewed recommendations that should be beneficial to regulatory agencies, health systems and providers involved as this public health crisis continues.

Recommendations for Regulators, Payors, Institutions, Medical and Physicians Societies, Health Systems and Broader Health Care Workers

As of last week, more than 70 test developers had informed FDA that they have a serological test available. Under the current EUA (Emergency Use Authorization) guidelines for serology assays, this means they are free to sell their assay on the market after informing the FDA. So far FDA has also approved only 4 of these assays, while the agency also cautioned that some test developers were making false claims. We have also heard about many disappointing initial experiences with the first-generation immunoassays, and physicians are already asking what a positive, or negative, immunoassay result means, particularly in the context of a compelling clinical history but no RT-PCR confirmation. We are hearing about false negatives, conflicting results based on different assays, poor delivery of results and most of all, lack of translation of the significance of positive results to clinical protection.

Based on our research, we found that the following recommendations could prove highly effective in delivering a rapid and smooth testing ramp for serological assays for COVID-19. We see the potential for regulatory agencies, payors, large health systems, academic institutions and the broader societies appreciating the approach.

1. **Incentivize labs by increasing reimbursement for the central lab titer based serology assay**: Incentivize by raising the CoVID-19 serology assay reimbursement from $15-$25 range to 2x or 3x in order to incentivize assay servicing labs including national reference labs to ramp up testing capacity for high quality central lab assays with titers.

Further expansion of reimbursement to manufacturers could also provide add-on payments to incentive manufacturers

2. **Incentivize manufacturers by increasing reimbursement for lateral flow assay that deliver high performance in independent validated studies:** Lateral flow assays provide rapid point of care testing without any instrument, are easy to administer in clinic or potentially in home setting, but early versions are generally plagued with performance and reproducibility challenges. The FDA is finally working with the NCI to validate these serology assays. That independent validation remains a key here and should give confidence to participants from physician to patients.
3. **Develop a central testing test registry and biobank:** A central testing registry combined with a biobank, similar to efforts such as UK Biobank, ensures that COVID patients' EHR records are available and samples are bio-banked for future research. Such biobanks are already being setup for All of US research program in the U.S. and extending it to collect COVID-19 samples appears feasible.
4. **A Central Dx committee for diagnostics that oversees test manufacturers and their supply chains**: Setup a central committee or a group of pathologists, lab professional and industry experts that identify challenges in supply chain before they become a bottleneck. The responsibility of this central committee must include monitoring of reagents and instrument supply chains. The COVID-19 testing labs will be required to report their inventory during the epidemic and the Dx committee will hold purchasing and negotiating power to bulk purchase directly from the manufacturer and deliver or ration to the labs as needed.
5. **Standardize Targets and Results**: Initially the FDA allowed any assay to be approved, provided it can be delivered. This created chaos in the marketplace and in the medical system. Most providers we talk to say that they believe we are "back to square one" in terms of having a reliable assay with clinically meaningful information. We believe that regulators have an obligation and a responsibility to establish a standard for diagnostic manufacturers to meet. This standard should be based on the totality of data available to the FDA. This standard should specify what the assays are measuring (e.g. S1 protein), the reliability of that target (e.g. RBD plus S1 is better than S1 alone, RBD + S1 + S2 may be even better). Even more importantly the standard should establish a level of antibody that can be reasonably expected to be as protective, or more protective, than clinical infection. This level of antibody should, over time, be prospectively qualified as evidence of clinical protection, although such information will not be available for several months. Unless the FDA takes this step, antibody testing will turn into another mess, and potentially an even worse mess than we encountered with direct viral detection assays.
6. **Patient resource for testing sites and testing modality**: A number of tests including point of care to central labs and both RT-PCR molecular and serology exist on the market but patients seeking such assays are unable to locate such tests. An online portal is needed that provides locations based on query and provides assay type, turnaround time and availability of tests.

7. **Mobile phlebotomy service**: For both symptomatic and asymptomatic patients, a mobile phlebotomy service would be most effective during times of epidemic. These phlebotomy services are available from private companies but should be viewed as an incremental tailwind for overall serology testing volumes as they offer blood draws at patient's homes, offering potential volumes for both seroprevalence studies and getting patients back to work.
8. **Establishing testing algorithm:** Establishing and publishing a testing algorithm is essential in the long run, especially regarding performance of serology assays that require reflexing to molecular assay. Clear testing algorithms should be established so they can widely followed by the providers.

Chasing the Antibody Reponses to COVID: A Brief Background

In response to a pathogen such as SARS-CoV-2 virus, the body mounts an immune response, with three key antibodies: IgM, IgG and IgA. Each individual antibody has different characteristics, including the time at which they begin to develop, the abundance of the antibody itself, and the duration for which it lasts. Serology tests emerging in the market are primarily focusing on IgG and IgM given their response timing and prevalence. A typical immune system response begins with the development of the IgM antibody in immediate response, followed by IgG which typically has a longer lasting and more abundant presence.

IgM antibodies are the first ones to be produced by the immune system in response to an antigen. The IgM antibody has a higher molecular weight and is expressed during the development of B cells in the primary immune response. Although it has 10 antigen binding sites (pentamer structure) the IgM's greater molecular weight and lower affinity results in quicker fall off of abundance. Despite being the first to respond, serology tests have focused less on detecting IgM antibodies at this time given the lower concentration in serum (5%-10% of serum immunoglobulin content). IgM antibodies typically have a short window and are eventually replaced by IgG. This occurrence results in the need for precise timing of an IgM focused assay to detect early indications of recovery or immunity to a virus. The detection of IgM does not necessarily mean presence of the target antigen; given the early response of the antibody to any antigen, excessive false positives may be reported.

IgG response begins after the IgM response, is more durable, with IgG being the most abundant type of immunoglobulin. While IgG is produced in the later stages of response, it is one of the best classifiers of recovery and potential immunity to a specific antigen. Furthermore, IgG has been shown to last longer in the system, allowing for continued detection over a certain time, while assuring an individual has proper antibodies to fight re-infection. IgG antibodies have two binding sites, making the monomer shape, and weighs significantly less than IgM antibodies. It acts as the main blood antibody of secondary responses and lasts for a significantly longer period of time. Extended presence of antigen specific IgG antibodies are a strong sign of immunity for an individual and given their greater prevalence (75%-80% of serum immunoglobulin content), are easily detectable.

IgA represents the remaining ~15% of total immunoglobulins in the serum. IgA primarily provides protection against infection in mucosal areas, such as the respiratory and gastrointestinal

tracts. Similar to IgM however, IgA has a short half-life, hampering its long-term utility. IgD and IgE are two other antibodies that can be found in an individual, however have minimal presence in a sample, generally 0.2% or less**.**

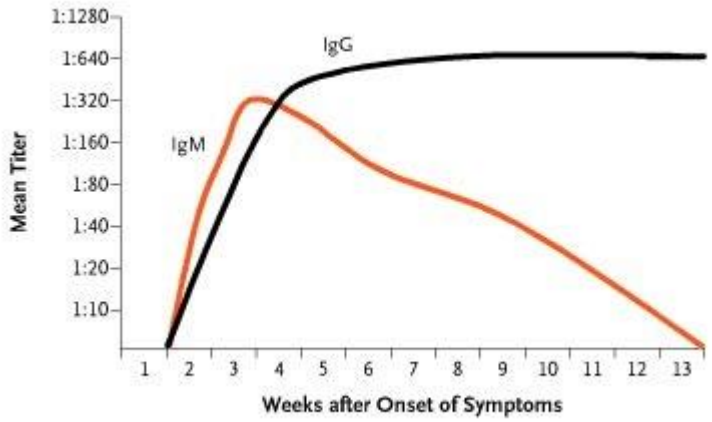
Figure 5. Timing of the Antibody Response

Days	IgM	IgG	IgA	RT-PCR Molecular Assay
1	N	N	N	Virus detected
3 - 5	Early Response	N	Early Response	
7 - 10	Peak	Early Response	Peak	
10 - 15	Declining	Ramp	Peak	

Source: SVB Leerink

Quantifying antibody titers is a differentiator to the immunoanalyzer method, discussed later in this note, as understanding the relative levels of each antibody are important to understand an individual's degree of response to the antigen. A greater IgG titer may suggest that one individual had a stronger response to the antigen than another, which may result in stronger immunity to re-infection of the specific virus. This occurrence remains to be seen in COVID-19 given the relative early stages of the outbreak and minimal antibody response information, however it will likely be a key point to understand as secondary and tertiary waves of infection begin in the coming years.

Figure 6. Changing titers of IgM and IgG to SARS-Associated Coronavirus from onset of illness through convalescent phase



Source: NEJM July, 31 2003

Serology Testing is Generally Conducted by Two Methods

As mentioned, there are two ways serology tests can be run: by lateral flow or on an immunoanalyzer. Both methods have their respective advantages and disadvantages, mainly on the level of information the test gives and the total turnaround time of each.

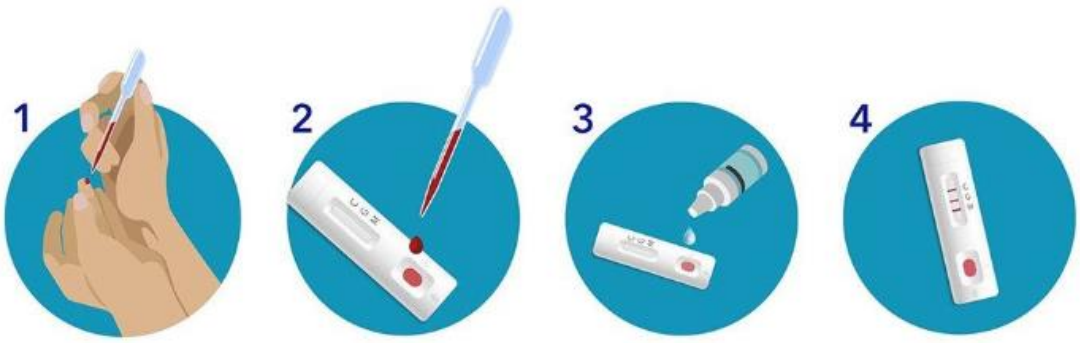
Strip based lateral flow testing: Lateral flow testing utilizes a finger prick blood sample dropped on to the testing stick, along with a few drops of sample buffer to initiate the reaction. Typically, within 10-15 minutes the strip will identify the presence of the target antibody. The below process flow and results graphics are from BioMedomics, who along with BDX (MP), and Henry Schein, is manufacturing and commercializing a serology based COVID-19 assay.

Lateral flow assays offer key information within minutes, but the overall effectiveness could take time to develop. A key advantage of the lateral low, strip-based test, is the rapid inherent turnaround time. These tests can offer results on the presence of antibodies within minutes, and in many cases can provide information on the presence of multiple antibodies, in this case typically IgM and IgG in a single test. Problems do arise however, as these tests only provide qualitative yes or no answers, only informing on the presence of the antibody rather than its abundance at that point in time.

Lateral flow assays require high performance and scalability for population scale studies. Ultimately, these assays are likely to be used in broad population settings, with a focus on maximizing volumes, and may potentially be followed up with a central lab based immunoassay for confirmation and/or additional information. Given the relatively inexpensive nature of these assays, they are likely to be used as a method of mass and frequent testing such as those in population studies.

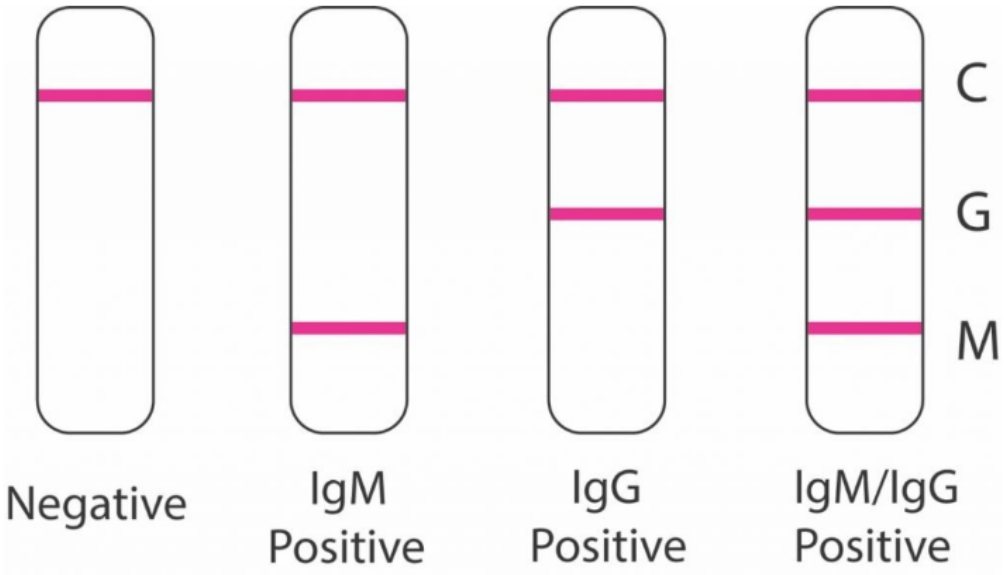
Ultimately, for success in this space, we expect a proven ability to scale production of assays while demonstrating consistently high performance. At this time, the market is flooding with lateral flow options, which has created unnecessary confusion on the initial roll out of these tests.

Figure 7.Lateral flow serology testing process



Source: BioMedomics

Figure 8.Example of results from a dual IgG and IgM serology test

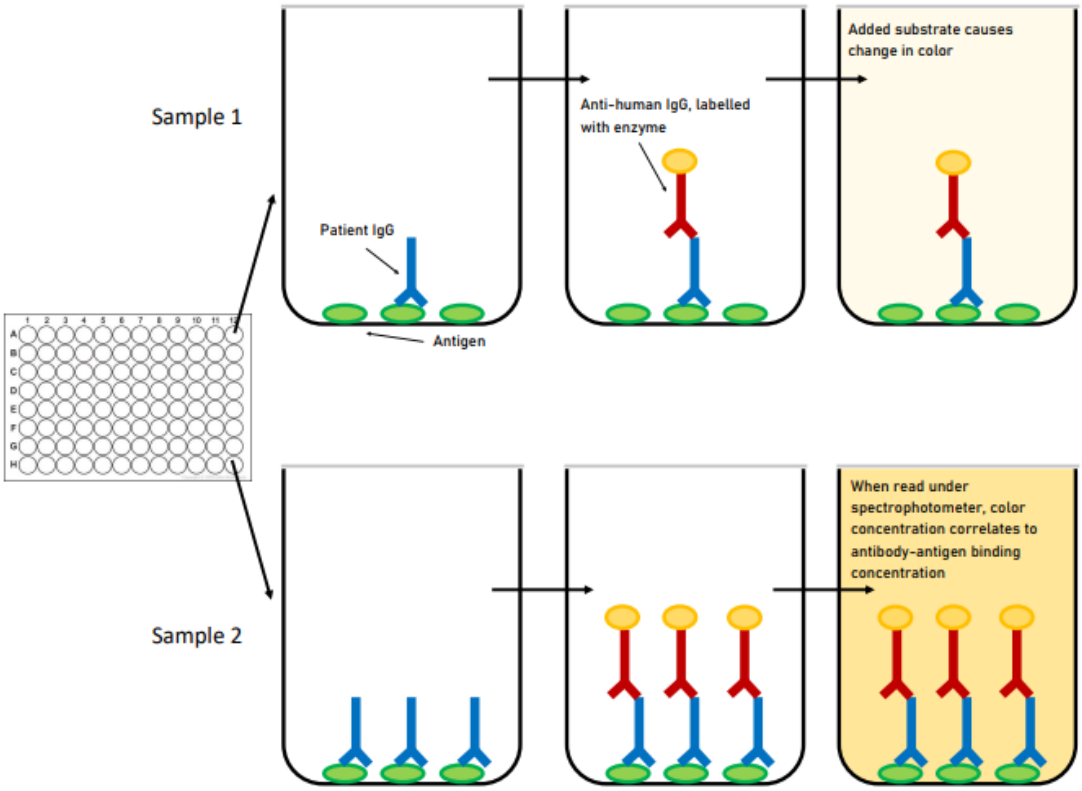


Source: BioMedomics

In contrast to the lateral flow method, central lab testing via immunoanalyzers offers more in-depth information at the cost of turnaround time. Given the need to ship samples to central labs for testing, turnaround times are longer, likely multiple days, however staying under one week. As seen with initial RT-PCR testing, should central labs see rapid ramp in volumes for serological assays, we would anticipate likely logistical delays as labs work towards efficiency and backlog elimination. A key advantage to the central lab message is a more quantitative answer. Understanding the level of antibody response in an individual is key to determining their true recovery and/or immunity to the virus, while also likely providing increased accuracy given the additional performance of an immunoanalyzer.

In enzyme linked immunosorbent assays (ELISA), the assay uses whole blood, plasma or serum sample and a plate coated with the viral protein of interest (Spike protein). Samples are incubated with the protein, which bind together in the presence of the antibodies. This bound complex can then be identified with a wash of antibodies that produce a fluorescent based read out, allowing for quantitative results. In some cases, such assays can be formatted to detect multiple proteins (multiplex), which may ultimately have more utility in COVID-19. Other proteins beyond the now-standard S1 protein could increase the sensitivity and specificity of the assay in this disease.

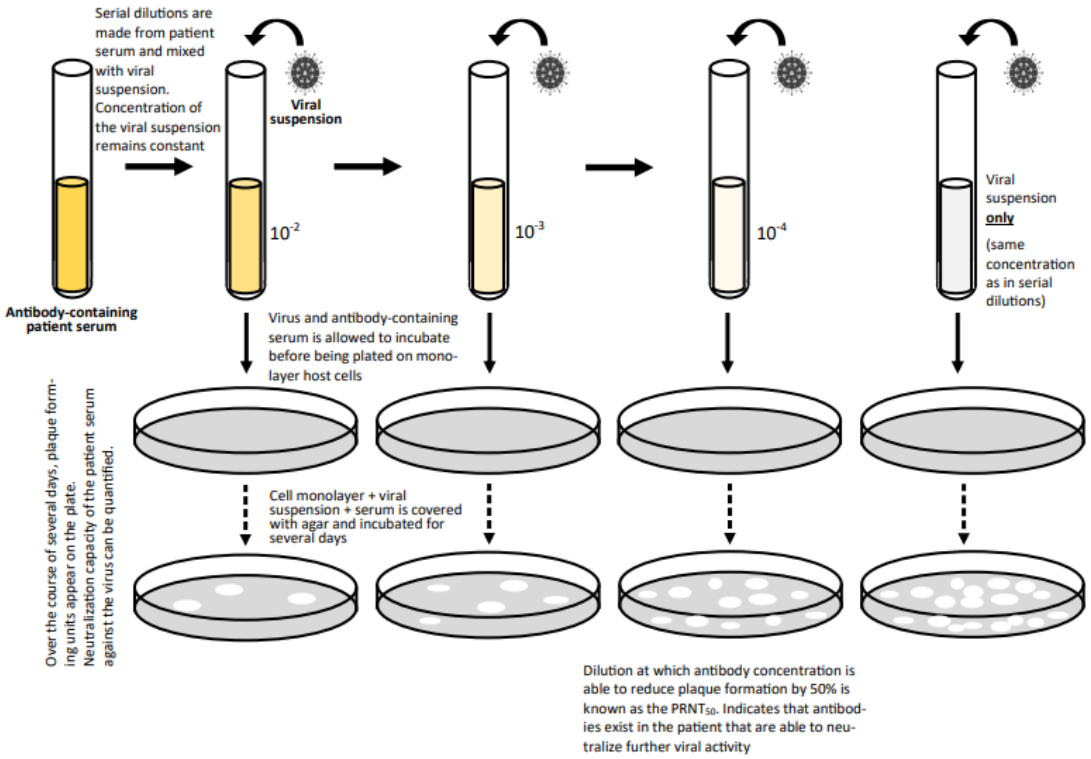
Figure 9.ELISA Process Flow



Source: Johns Hopkins

A third test strategy is less common: Neutralization assays. Neutralization assays are run in a lab setting and rely on patient antibodies to prevent viral infection. These assays are able to tell if a patient has antibodies that are both active and effective against the virus, even after the patient has recovered or cleared the virus. In a neutralization test, researchers grow the virus and cells with decreasing concentrations of patient antibodies to visualize and quantify how many antibodies in patient's serum are able to block the replication of the virus. This occurs when the antibody binds to an important cell entry protein on the virus, or in the case of SARS-CoV-2, the ACE-2 receptor. The assay takes longer than central lab assays in turnaround time.

Figure 10.Neutralization Process Flow



Source: Johns Hopkins

Ultimate paradigm likely to include a combination of lateral flow and central lab testing. With each method having its own advantages and disadvantages, we anticipate an ultimate need for both. Receiving a rapid qualitative answer offers the ability to take quick actions to continue distancing while awaiting a central lab assay at a relatively low cost, likely under $20 for a lateral flow test. A combination of both testing methodologies, potentially both tests for each individual, is likely in the coming months as more tests come to market and continued validation identifies the better performing assays, further defining the ultimate path taken. Success in this space is key for managing secondary and tertiary waves of the virus, which at this point appear inevitable, while at the same time offering a better understanding of differing responses among different individuals.

Collectively, both methods of serology testing target a much larger population, with a number of indications in focus. The multi-indication testing focus collectively requires high performing, rapid turnaround assays with the ability to scale to the tens of millions in the near term, likely utilizing both the lateral flow and central lab methods, compared to the diagnostic RT-PCR assays which required more development and validation and have taken longer to ramp to current levels.

Figure 11. Serology Testing has Specific Advantages and Utility vs. Molecular Test also known as RT- PCR for COVID-19

	COVID-19 RT-PCR Assay	COVID-19 Antibody (Serology) Assay
Need/Use Case	• Infected phase, diagnose virus	• Rapid antibody detection for recovery/immunity
Indications	• Confirming COVID-19 diagnosis	• ID immunity for back to work • ID recovered pts to donate conv. Plasma • Broad based population screening • Confirmation of vaccine efficacy
Analyte	• Nasal or oral swab	• Blood or plasma
Turn-around	• Hospital Lab: 1-2 days • Central Lab: 3-4 days including logistics	• Lateral Flow: 10-15 minutes • Central Lab: 3-4 days including logistics
Performance	• 70% sens vs. CT 98% • 95%+ spec	• Likely to require 95%+ sens/spec • Ultimately depends on virus prevalence
Price	• ~$50, recently increased to ~$100	• Lateral Flow: $5 - $20 • Central Lab: ~$50
Market Size	• Currently ~3M+ cumulative tests in US • Likely to reach 10M test capacity in ST	• Still to be determined • 50% penetration (to US population) at $25 implies $4.1B opportunity

Source: SVB Leerink

Sizing the Potential COVID-19 Serology Market (US)

While the market size and price per test is likely to vary based on the indication of focus, we anticipate a significant portion of people will likely take a COVID-19 serology test in the next few years. We use $15 - $25 price per test range in our model, assuming a mix of both lateral flow strip-based assays costing $5-$10 per test, and assays that are run at a central lab, which we expect to be in the $25 - $50 range. Since surpassing 1,000 cumulative RT-PCR tests on March 5, 2020 (COVID Tracking Project), the United States has run over 3.7 million tests (as of April 19, 2020), suggesting significant efforts to scale this more complex, longer turnaround test, which has been mostly restricted to symptomatic patients and their close contacts.

Figure 12.COVID-19 Serology Market Estimate (US)

US Serology Market Opportunity												
Percent of population	10%		15%		20%		25%		50%		75%	
Total Volume	33M		49M		65M		82M		164M		245M	
Cost per Assay	$15	$25	$15	$25	$15	$25	$15	$25	$15	$25	$15	$25
Total Market Opportunity	**$0.5B**	**$0.8B**	**$0.7B**	**$1.2B**	**$1.0B**	**$1.6B**	**$1.2B**	**$2.0B**	**$2.5B**	**$4.1B**	**$3.7B**	**$6.1B**
US Population	327M											

Source: SVB Leerink

This market remains relatively unproven given its infancy and could ultimately end up on the larger side if immune protection from the antibodies was not as durable and thus these tests could be required annually – making it a large market longer-term.

Figure 13. Sizeable Manufacturers Step Into the Market with Potential for High Volume Tests on Fully Automated Immunoanalyzers

Company	COVID-19 RT-PCR Assay	COVID-19 Serology Assay
Abbott	• Fully automated on m2000 (EUA) • Point of Care on IDNOW (EUA)	• Announced launch 04/15/2020 (Central/Core lab)
BDX		• Announced 03/31/2020 with BioMedomics (Lateral Flow)
Danaher	• Point of Care on GeneXpert (EUA)	• Announced development on 03/31/2020 (Central/Core lab)
DiaSorin	• Semi-Automated on Simplexa (EUA)	• Announced launch 04/07/2020 (Central/Core lab)
Roche	• Fully automated on Cobas (EUA)	• Announced development of Elecsys antibody assay with expected launch early May (Central/Core lab)
Siemens		• Likely to announce on Atellica System

Source: SVB Leerink, FDA, Johns Hopkins

Figure 14. FDA Emergency Use Approval Beginning to Come Through in Serology

Company	EUA Date	Methodology	Antibody Target	Notes
Mount Sinai	4/15/2020	ELISA	IgG	Limited to use at Mount Sinai Laboratories, Center for Clinical Laboratories, a Division of Dept. of Pathology, Molecular, and Cell-Based Medicine at the Icahn School of Medicine at Mount Sinai
Ortho Clinical Diagnostics	4/15/2020	Modified ELISA	IgM, IgG	Detects total IgM and IgG but does not discern between the two. For use on VITROS family of systems.
ChemBio	4/15/2020	Lateral flow	IgM, IgG	Produced 20M HIV tests in 2019, shifting focus to COVID-19, hiring 100 people in manufacturing, quality control and engineering
Cellex, Inc	4/1/2020	Lateral flow	IgM, IgG	93.8%/95.6% sens/spec when tested at 2 Chinese hospitals on 128 COVID-19 positive patients and 250 COVID-19 negative patients.

Source: SVB Leerink, FDA, Company Websites

Serology Testing History: What Have We Learned From HIV?

Though HIV and COVID-19 are different diseases, the idea of a serology test to identify the presence of antibodies is one in the same. After the initial description of HIV in 1983, it took two years for the "first generation" antibody test to come to market. This first-generation assay detected IgG antibodies to the HIV-1 virus only, and demonstrated high sensitivity (99%), though suffered from an antibody-negative window of 8-10 weeks, and potentially up to 12 weeks. The high sensitivity was helpful for protecting the blood supply, however led to false positive when testing low-risk individuals, associated with infections, autoimmune disease, pregnancy, and other unspecified conditions. As a result, a second level of testing was added to improve specificity levels, with the algorithm now including a Western blot assay and HTLV III immunofluorescence assay (IFA). In summary, this first-generation assay suffered from positive predictive value that could be lower than 50% in lower risk populations.

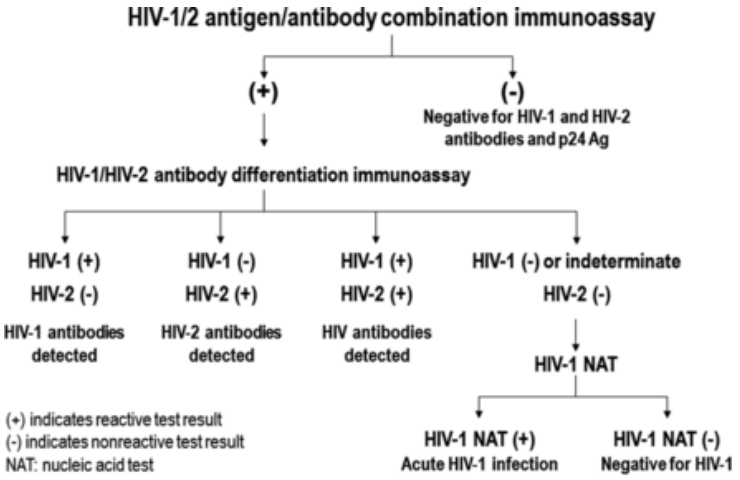
Over the next 6 years, two new generations of HIV antibody tests were developed. The second-generation assay reduced the antibody negative window down to 4 to 6 weeks post infection as they were able to detect the HIV-2 antibody in addition to HIV-1. When combining IgG and IgM, the test reduced the antibody-negative period to 3 weeks. These second and third generation tests saw further improved sensitivity to 99.5%+, while specificity increased to 99%+.

These marginal improvements continued in 1997, with a fourth-generation assay that combined antibody and antigen detection. Despite both antibody and antigen detection in these procedures, the test would only give a single result, not differentiating what was driving a positive result. In 2010, **Abbot's ARCHITECT** was cleared by the FDA as a fourth-generation test and was found to have near 100% sensitivity and repeat testing specificity of 99.5% in a cohort of

3,386 HIV-infected individuals, 7,551 uninfected subjects, and 58 with acute HIV infection (Chavez et al.). In 2011, Bio-Rad followed with the GS ELISA system clearing FDA review, showing 100% sensitivity and 99.9% to 100% specificity on 9,150 specimens. In 2015, Siemens ADVIA fourth-generation assay was approved, showing antibody sensitivity of 100%, antigen sensitivity of 97.87% and a specificity of 99.69% (FDA, LINK).

With the advance of the fourth-generation assay into the US in the early 2010s, a new testing algorithm was needed. Given a 4-6-week antibody negative window with Western blot, false negatives in patients with early infection were a possibility, resulting in the Western blot being replaced by a differentiation assay. The US CDC had initially proposed two separate algorithms, separating low and high risk for infection, however in 2014, the single algorithm below was finalized.

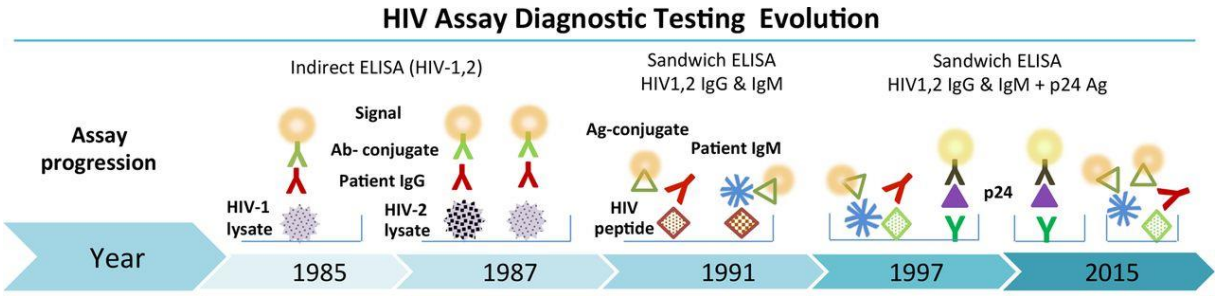
Figure 15. CDC's Fourth-Generation HIV Antibody Testing Algorithm



Source: American Society for Microbiology

In 2015, the FDA approved Bio-Rad's BioPlex 2200 HIV Ag/Ab fifth generation HIV screening test. This test detects both HIV antibody and the HIV-1 p24 antigen, but provides a separate analysis for each analyte, going one step further than the fourth-generation assay. A new algorithm is required as there is no need for differentiation of antibody positive specimens as the test already provides separate results for HIV-1 and HIV-2 antibody, and specimens that are reactive only to the p24 antigen do not require antibody confirming procedures. This assay was evaluated by Salmona et al. and found to have 100% sensitivity and 99.5% specificity in a study of 1,505 patients.

Figure 16. HIV Antibody Diagnostic Pathway From 1985 to Present



Generation	1st	2nd	3rd	4th	5th
Antigen (Ag) Source	Virus Infected Cell Lysate	Lysate & Recombinant	Recombinant & Synthetic peptides	Recombinant & Synthetic peptides	Recombinant & Synthetic peptides
Specificity	95-98%	>99%	>99.5%	99.5%	99.5%
Sensitivity	99%	>99.5%	>99.5%	>99.8%	100%
Negative Window	8-10 weeks	4-6 weeks	2-3 weeks	2 weeks	2 weeks
Detects Antibody (Ab) and Ag	IgG Anti HIV-1	IgG anti HIV-1 and IgG anti HIV-2	IgG and IgM anti HIV-1, HIV-2 and Group O	IgG and IgM anti HIV-1, HIV-2 and Group O. Also detects HIV-1 p24 Ag	IgG and IgM anti HIV-1, HIV-2 and Group O. Also detects HIV-1 p24 Ag
Results	Single result	Single result	Single result	Single result; does not differentiate Ab from Ag positivity	Separate HIV-1 and HIV 2 Ab and Ag results
Confirming Tests	HIV-1 western blot (WB) or immunofluorescence (IFA)	HIV-1 WB or IFA, HIV-2 ELISA and WB if HIV-1 confirm is negative	HIV-1 WB or IFA, HIV-2 ELISA and WB if HIV-1 confirm is negative	HIV-1.2 differentiation Assay followed by qualitative HIV-1 RNA PCR if differentiation assay is negative	Not determined at the time of this writing

Source: American Society for Microbiology

A Long History of HIV Antibody Testing Can Influence the COVID-19 Serology Pathway

As can be seen above, the HIV antibody testing pathway ranged over 30 years of research and development, with tests becoming more in depth and accurate with each generation. We believe there are multiple takeaways from the HIV pathway, the most important being that a COVID-19 serology assay is not going to be perfect, especially in the early stages, but we see potential for significantly shortened timelines. The FDA has yet to set any guidelines on serology tests in terms of performance, though we can see above HIV testing started with relatively high specificity and sensitivity, however suffered from longer antibody negative windows. Given the depth of research in serology testing since 1985, and more recently with efforts made to further enhance HIV testing, we believe similar levels of performance are achievable, however the expedited timeline is likely to sacrifice performance in the early stages of development and roll out.

COVID-19 Serology Testing: Where Are We Headed?

Following our analysis of the ongoing situation and past experiences, we feel positive about the ABT serology data presented so far, but still have a number of questions that remain to be answered. With the lengthy journey of HIV diagnostics, our KOL conversations, and industry feedback, we are clearly working on an expedited timeline. That being said, we do recognize that there are key questions that must be answered, mainly by the FDA, in order to efficiently advance development and commercialization efforts. **Key questions, and our hopeful answers include:**

1. **FDA leniency has created a flood of un-validated tests on the market, what can be done to clear up confusion?**
    a. The FDA has highlighted accuracy as a "very" important issue. In their recent weekly webcast, FDA representatives highlighted that they continue to welcome EUA submissions for point of care and high-volume central lab assays, acknowledging that both will be necessary to address anticipated volumes. When discussing accuracy concerns, the administration highlighted a voluntary validation program to address and verify accuracy of tests coming to market. Developers can voluntarily participate in the program by sending point of care test kits and the necessary instrumentation to a central location where a team of independent researchers will run a panel of positive and negative serum/plasma samples to observe the performance of the assay. While this program is voluntary, we do not expect any tests that come to market without undergoing this independent validation, or another of its kind by a regulatory body, will gain any traction in the marketplace. It's clear that the FDA needs to do more to provide standards and guidelines which can be used across immunoassays from different companies. FDA also needs to provide education on how to interpret the positive results and how immnoanalyzer results compare to the lateral flow results. The economic impact from FDA not acting sooner created significant challenges in the initial scale up, and healthcare industry participants expect the same could be at risk in serology.
2. **What is the ideal pathway on the first iteration of serology testing?**
    a. With four potential indications, as of now, for serology testing, we anticipate initial roll out of tests will focus on identifying recovered patients who can donate convalescent plasma and determining who is able to return to work, with broad based population testing and confirmation of vaccine efficacy being longer term goals. The divide between lateral flow, strip based, assays and central lab assays run on immunoanalyzers remains to be seen. Titer information is likely key for identifying patients that are able to donate their plasma to currently sick patients, thus central lab testing is most likely to be favorable in this case. For a "get-back to work" test, a high performing lateral flow assay is likely possible, however we believe ultimately it will be a two-step process, with a lateral flow test providing a quick response followed by a central lab test. As lateral flow assays are currently targeting point of care administration (i.e. not self-administered), we expect the ease of drawing a vile of

blood for central lab testing will be possible at the same time, though ultimate capacity of tests to be run on immunoanalyzers throughout the country is uncertain at this time.

3. **What is a target benchmark for initial tests? Both lateral flow and central lab?**

    a. Test performance is a key metric. As we can see above, the first-generation HIV serology assay achieved 99% sensitivity (1% false negative) and 95% - 98% specificity depending on the assay and data set. Abbott data so far suggests even better performance vs HIV, but it remains to be seen if that holds up with multiple independent evaluations. The KOLs suggested that 90%+ sensitivity and specificity is a good starting point for the first generation of COVID-19 serology tests, though will ultimately need to move higher over time for more assurance in negative and positive results.

    From a positive predictive value (PPV) and negative predictive value (NPV) viewpoint, disease prevalence comes into play. PPV is calculated as the probability that following a positive test result, that individual truly has the specific disease. NPV on the other hand is calculated at the probability that following a negative test result, that individual truly does not have the specific disease.

    For any test, sensitivity and specificity remain the same, assuming the inputs to the test are locked, while PPV and NPV change with prevalence of disease. As prevalence increases, PPV increases as there are more true positives for every false positive, while NPV decreases as there are more false negatives for every true negative. In the case of COVID-19, disease prevalence remains unknown, however an increasing prevalence of disease creates less of an issue with test performance. For example, if disease prevalence reaches 80% of the population, the positive predictive value would be extremely high as odds are that an individual has had the disease, while a person who tests negative is statistically more likely to actually have the disease, thus a false negative.

Figure 17. Test Performance Formulas

Performance Calculations			
Sensitivity =	$\frac{\text{True Pos}}{\text{True Pos + False Neg}}$	Specificity =	$\frac{\text{True Neg}}{\text{True Neg + False Pos}}$
PPV =	$\frac{\text{True Pos}}{\text{True Pos + False Pos}}$	NPV =	$\frac{\text{True Neg}}{\text{True Neg + False Neg}}$

Source: SVB Leerink

Figure 18. NPV and PPV outcomes in the Tested Population Based on Assumed Sensitivity, Specificity and Prevalence of Disease

NPV and PPV Assuming 90% Sensitivity and Specificity						
Prevalence	1%	5%	10%	25%	50%	75%
NPV	99.9%	99.4%	98.8%	96.4%	90.0%	75.0%
PPV	8.3%	32.1%	50.0%	75.0%	90.0%	96.4%
Sensitivity	90%					
Specificity	90%					

NPV and PPV Assuming 95% Sensitivity and Specificity						
Prevalence	1%	5%	10%	25%	50%	75%
NPV	99.9%	99.7%	99.4%	98.3%	95.0%	86.4%
PPV	16.1%	50.0%	67.9%	86.4%	95.0%	98.3%
Sensitivity	95%					
Specificity	95%					

NPV and PPV Assuming 99% Sensitivity and Specificity						
Prevalence	1%	5%	10%	25%	50%	75%
NPV	100.0%	99.9%	99.9%	99.7%	99.0%	97.1%
PPV	50.0%	83.9%	91.7%	97.1%	99.0%	99.7%
Sensitivity	99%					
Specificity	99%					

Source: SVB Leerink

4. **What are the consequences of sacrificing performance for speed to development?**

    a. As with any disease, there are consequences with false positive and false negative results. In the case of COVID-19 antibody testing, we see a larger consequence with a false positive result. Patients that test positive for having the presence of the target antibody, likely IgG and/or IgM, may have a false sense of safety or immunity when going out in public, or back to work, when they are actually vulnerable to becoming infected by the disease and spreading to others. With a false negative result or identifying a patient who does not have the target antibodies, the end result would be continued social distancing until a level of herd immunity is reached, making the environment safe for all. As mentioned earlier, a separate problem arises here with people who have taken appropriate isolation measures during the pandemic not being exposed to the disease not being able to return to work. Ultimately however, we expect serological assays will have more impact in future waves of the virus, and enable better understanding of one person's response to the disease compared to another, as well as an idea on the duration of immunity for people who have recovered.

5. **What are the initial goals of serology testing?**
    a. Initial roll out of serology tests are likely to focus on identifying patients who have recovered that are able to donate their convalescent plasma to currently sick patients to aid antibody production to fight the virus. This indication has a much smaller scale requirement and more urgent need. Over the next few months, as developers begin to focus on scale and commercialization of their assays, we anticipate the focus will shift to testing workers that are able to safely return to work, followed by broad population screening to determine the full spread of the virus and testing in vaccine development to confirm efficacy. As we expect COVID-19 could be a recurring and maybe seasonal disease, testing as we move into future waves of the disease is likely to continue to grow in importance, especially for determining the length of seroprotection among patients who have recovered.
6. **What are the long-term expectations for future generations of serology testing?**
    a. As seen with HIV antibody testing, performance of their first-generation assay was strong, with over 95% specificity and 99% sensitivity, however the biggest challenge was the antibody negative window of 8-10 weeks. Over time, specificity and sensitivity of the test continued to improve as the algorithm began including additional antibody targets and more confirming tests, which likely moved in parallel with advancement in technology and research capabilities. Given the attention to COVID-19 and the impact it is already having on the world, we expect developers will remain focused on improving their assays in the near term, and expect a much shorter generational gap than was seen with HIV testing, which continues to see incremental improvements 30 years later.

FDA Emergency Use Authorization Negates Need for IVD During COVID Times

Typically, diagnostic assays are developed in a lab, initially for internal use, as a Lab Developed Test (LDT), or directly as an in-vitro diagnostic (IVD) by commercial developers. In normal circumstances, for a lab developed test to be used internally (in the lab it was developed), labs must have a CLIA (Clinical Laboratory Improvement Amendment) license. This pathway enables a lab to forgo the IVD approval path for every test they develop. A CLIA license includes demonstrated testing proficiency, lab director and operator certificates and an established criterion for test validation. This option ensures accuracy, reliability, and timelines of test results regardless of where a test was performed and allows for quicker development timelines by avoiding FDA IVD approval.

Occasionally, a CLIA lab with an LDT may opt to continue to IVD approval to commercially ship their test kits throughout the country. Furthermore, large scale test developers also pursue the IVD route, which include a more rigorous validation by the FDA prior to approval. These IVDs are sold as complete kits, including all procedures and controls needed to perform the

test. This approval is typically required pre-commercialization, leading to occasionally long development timelines for an IVD assay.

Following the outbreak of COVID-19, the FDA authorized the emergency use of in vitro diagnostics for detection or diagnosis of COVID-19. The FDA can issue Emergency Use Authorizations (EUAs) to make diagnostic tests readily available in a short amount of time without the typical IVD approval process. This effort has enabled a quick response to initial molecular testing hiccups in the United States, with multiple companies introducing RT-PCR testing kits for use in diagnosing COVID-19. Test developers were, and are, allowed to market and certified labs allowed to run a test without having filed for EUA, provided they file for approval within 15 days after validation.

As the conversation has shifted to less complex antibody testing, FDA guidelines are more lenient. Given the lesser complexity of a serological test vs RT-PCR, the FDA has allowed developers to begin to market or use their tests once appropriate evaluation of accuracy and reliability has been done, without prior FDA review. While these recommendations don't even require the need to file for EUA, the FDA is still accepting submissions, and we do not expect significant adoption of any test that does not have EUA or other forms of independent verification.

Who is Likely to Win Longer-Term?

We have continued to expect that larger, more established and reputable test developers will drive the total serology volumes despite increasing numbers of tests coming to market. As highlighted throughout this note, we, along with KOLs, have been relatively skeptical of smaller companies being able to scale production of their tests. With recent announcements and data from Abbot and Roche, and expected launches from others including Danaher (Cepheid), DiaSorin, Siemens, and others, we anticipate a significant and quick volume ramp. Abbott suggested that they will be able to ship 4M tests in the second half of April, with the ability to ramp to 20M tests per month by June. Following Roche's recent announcement (04/17/2020) of a test to be available by early March, the company suggested that they expect to be able to ship 25M tests per week (100M per month), suggesting over 120M testing capacity per month from Roche and Abbott alone.

As of this writing, there are only four tests that have received Emergency Use Authorization in the United States, with many tests having been approved for use in other countries and looking for entrance in US markets. Based on current EUA requirements, test developers have 15 days to submit their assay for EUA upon completion of internal validation, though labs can begin using the assays prior to approval. Given the low complexity of a serology-based test, the FDA has been more lenient with their development measures, which has created a flood of tests available in the market, likely creating a more complex review process for labs. Based on conversations with KOLs, we believe many of these tests will end up being "junk" as performance data is not yet available, and limitations on being able to scale production are likely to dissuad labs from actually ordering the tests.

Company announcements highlight increasing focus on serology among larger players:

As the conversation has shifted to serological assays over the past few weeks, many smaller companies have announced tests, however the market will ultimately be driven by larger manufacturers. While there have been many serology assays announced, over 70 as of last week, we expect a majority of volumes to be driven by a few key players, some of which have already announced the availability (ABT) or development of their test (DHR, DiaSorin), and some who have not. Below, we highlight high level of assay availability from some of the larger players in the space, and recent newsworthy developments in serology.

Figure 19. Sizeable Manufacturers Likely to Impact the Market

Company	COVID-19 RT-PCR Assay	COVID-19 Serology Assay
Abbott	• Fully automated on m2000 (EUA) • Point of Care on IDNOW (EUA)	• Announced launch 04/15/2020 (Central/Core lab)
BDX		• Announced 03/31/2020 with BioMedomics (Lateral Flow)
Danaher	• Point of Care on GeneXpert (EUA)	• Announced development on 03/31/2020 (Central/Core lab)
DiaSorin	• Semi-Automated on Simplexa (EUA)	• Announced launch 04/07/2020 (Central/Core lab)
Roche	• Fully automated on Cobas (EUA)	• Announced development of Elecsys antibody assay with expected launch early May (Central/Core lab)
Siemens		• Likely to announce on Atellica System

Source: SVB Leerink, FDA, Johns Hopkins

Roche 04/17/2020: Announces development of Elecsys Anti-SARS-CoV-2 serology test with target availability in early May for countries accepting CE-mark and is actively pursuing FDA EUA. Test is for use on Roche cobas e analyzer family of instruments, which can provide test results in 18 minutes with total throughput up to 300 tests/hour. Conversations with the company suggest ability to ship 25M tests per week worldwide after launch.

Eurofins 04/17/2020: Announces CE-marking of a range of serology-based antibody detection testing kits, in conjunction with Gold Standard Diagnostics Inc, VIROTECH Diagnostics GmbH, NovaTec Immundiagnostica GmbH and Ingenasa, all well-established providers of testing solutions. Tests are intended for the qualitative detection of IgG, IgM and IgA antibodies to SARS-CoV-2 virus and demonstrated high specificity on initial testing of more than 200 healthy and potentially cross reacting samples.

Abbott Labs 04/15/2020: Announces the launch of their third COVID-19 test. This lab-based serology test is for IgG antibody detection and will be available on their ARCHITECT i1000SR and i2000SR instruments, of which there are over 2,000 currently in use in U.S. labs, that can run 100-200 tests per hour. Abbott expects to immediately ship 1M tests (last week), and 4M by the end of April (approx. 2-week period), with expectations of ramping to 20M tests in June and beyond.

Performance data for the IgG test is expected upon EUA review, and the test is expected to expand to IgM antibody detection in time. We believe this announcement speaks to the potential scale of serology tests from large developers and expect continued expansion and improvement over time.

Bio-Rad 04/07/2020: Announces availability of serology assay to detect COVID-19 antibodies that has shown 99%+ specificity on 700 samples. The test is currently undergoing clinical evaluation in several hospitals for further performance confirmation. The test was designed for use manually or on automated immunoassay platforms, such as Bio-Rad's EVOLIS System.

Quotient 04/06/2020: Announces completion of development phase of microarray based COVID-19 antibody test for their fully automated MosaiQ system that can process 3,000 antibody tests per day. Expected commercial ready research use only product in Europe week of April 12 with expectations of filing for CE Mark and FDA EUA approval upon readiness.

Biomerica/Mount Sinai 04/02/2020: Announce agreement to scale up lab version of a serological test. Combined, can run 1M ELISA microplate tests/month for as low as $10 per patient.

Becton, Dickinson and Co 03/31/2020: Along with BioMedomics announces point of care antibody test with less than 15-minute turnaround time. The test, which is available through BDX, is manufactured by BioMedomics and distributed by Henry Schein.

Danaher (Beckman Coulter) 03/31/2020: Announces they are developing an IgM and IgG antibody assay for use on their high throughput Access system.

Henry Schein 03/326/2020: Announces availability of antibody based rapid blood test Standard Q COVID-19 IgM/IgG Rapid Test for point of care administration manufactured by SDBiosensor.

Instrumentation Providers Most Likely to Benefit From Central Lab Testing

Roche

Roche has a number of instruments available for running immunoassays, most notably in our view is the Roche cobas e 801 module. This module fits in to their cobas 8000 series and can run up to 300 tests per hour. The lesser throughput 600 series, including the cobas e 601 and 602 can run up to 170 tests per hour with a menu of over 100 assays.

Figure 20. Roche cobas e 801 Module

Source: Roche

Abbott

Abbott's imunnoanalyzer family, Architect, spans three levels of instruments, with the largest (i4000SR) offering a maximum capacity of 400 tests per hour while the lower level i2000SR and i1000SR offer throughput of 200 and 100 tests per hour respectively. Given Abbott's Architect instrument covers a wide range of tests, including HIV and Hepatitis B serology tests, we expect that the company will follow suit with a serology based COVID-19 test.

Figure 21. Abbott Architect Imunnoanalyzer Instrument Family

Source: Abbott

Siemens

Siemens offers multiple immunoassay systems, including their Atellica, ADVIA and IMMULITE families. The Atellica system integrates their immunoassay and clinical chemistry analyzers with a new standard in sample management to focus on better outcomes, while the ADVIA and IMMULITE systems are targeted to immunoanalysis. All systems' menus include a variety of tests, including those for HIV and hepatitis, as we have seen with other instruments on the market. The ADVIA family includes the XPT, XP and CP (benchtop) systems, with a comprehensive menu of over 70 tests. The newer XPT is able to churn 240 tests per hour, with 18 minutes to first result

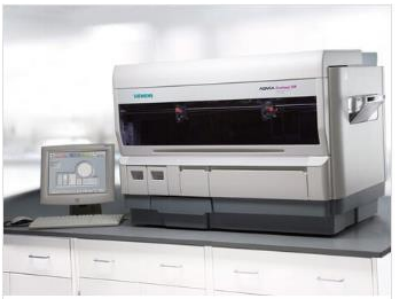
and then results every 15 seconds thereafter, while the smaller, mid throughput CP system can produce 180 tests per hour. Finally, the IMMULITE system, includes the 2000 XPi and 1000. The larger 2000 XPi offers one of the largest automated immunoassay menus available, with up to 200 tests per hour and 35 minutes to first result. The smaller 1000 has throughput of 1000 tests per hour with a time to first result of 42 minutes regularly, though can reach 15 minutes in “turbo” mode.

Additionally, in February of this year Siemens was announced as the preferred supplier for immunoassay testing at Quest Diagnostics, which will ultimately result in the largest deployment of their Atellica Solution worldwide. Quest committed to deploying 120 Atellica Solution immunoassay analyzers across 19 esoteric and core labs throughout the US. Quest is one of the largest core lab testing providers in the country, and this partnership offers Siemens direct access to a significant portion of ultimate imunnoassay testing for COVID-19 in our view.

Figure 22. Siemens ADVIA Imunnoanalyzer Instrument Family

ADVIA Centaur XPT Immunoassay System

ADVIA Centaur XP Immunoassay System

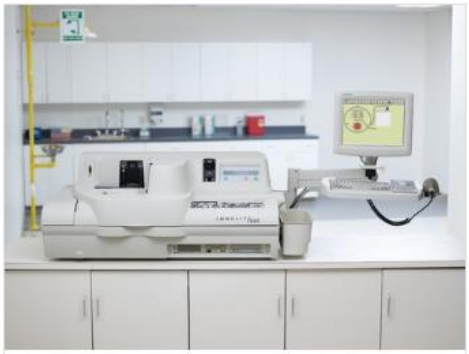


ADVIA Centaur CP Immunoassay System

Source: Siemens

Figure 23. Siemens IMMULITE Imunnoanalyzer Instrument Family

IMMULITE 2000 XPi Immunoassay System



IMMULITE 1000 Immunoassay System

Source: Siemens

Beckman Coulter

Danaher's Beckman Coulter's COVID-19 serology test is expected to be available on their high-throughput Access family of immunoassay systems, which includes the Access 2, and the Dxl series. The Access 2 instrument is capable of running up to 100 tests per hour while having one of the smallest footprints in its class across the industry. Beckman Coulter highlights over 10,000 instrument placements worldwide.

The larger Dxl Series (including the UniCel Dxl 600 and Unicel Dxl 800) have even higher throughput, with the larger 800 being able to perform up to 400 tests per hour, compared to 200 tests per hour for the 600.

Figure 24. Beckman Coulter (DHR) Access 2 Instrument

Source: Beckman Coulter

Figure 25. Beckman Coulter (DHR) UniCel Dxl 800 Instrument

Source: Beckman Coulter

Bio-Rad

The Bio-Rad Evolis system is a self-contained microplate processor. The "walkaway" eligible system can process up to 6 plates per worklist with 4 tests per pate, and a capacity of up to 180 primary tubes. Depending on the assay, the system can run up to 500 tests per shift, according to the company, with full automation following sample load. **Bio-Rad has been one of the few to**

disclose performance of their antibody test in development, suggesting initial performance of over 99% specificity (less than 1% false positive) on the first 700 samples.

Figure 26. Bio-Rad Evolis Instrument

Source: Bio-Rad

Quotient

Quotient's MosaiQ is a fully automated and consolidated testing platform for blood grouping and transfusion-transmitted infection screening of donated blood. The instrument, which has now pivoted to COVID-19 serological testing, can test 1,000 microarrays when fully loaded, delivering first results within 35 minutes and subsequent results every 24 seconds afterwards. The platform results include blood grouping, extended phenotyping, **antibody detection,** exclusion of clinically significant antibodies, and donor disease screening.

Figure 27. Quotient MosaiQ Instrument

Source: Quotient

DiaSorin

Diasorin has announced their expectations to have an antibody test on the market by the end of April. The serological test is expected to be run on their LIASON XL platform, which has an install base of ~5,000 worldwide, including more than 500 in Italy, where the company is based. This fully automated platform can allow labs to process up to 170 patient samples per hour with minimal intervention. While DiaSorin is not a large-scale manufacturer (compared to Roche, Abbot and Siemens), we believe they have a strong reputation and large install base that will enable ultimate adoption of their antibody test in labs throughout the world.

Figure 28. DiaSorin LIASON XL Instrument

Source: DiaSorin

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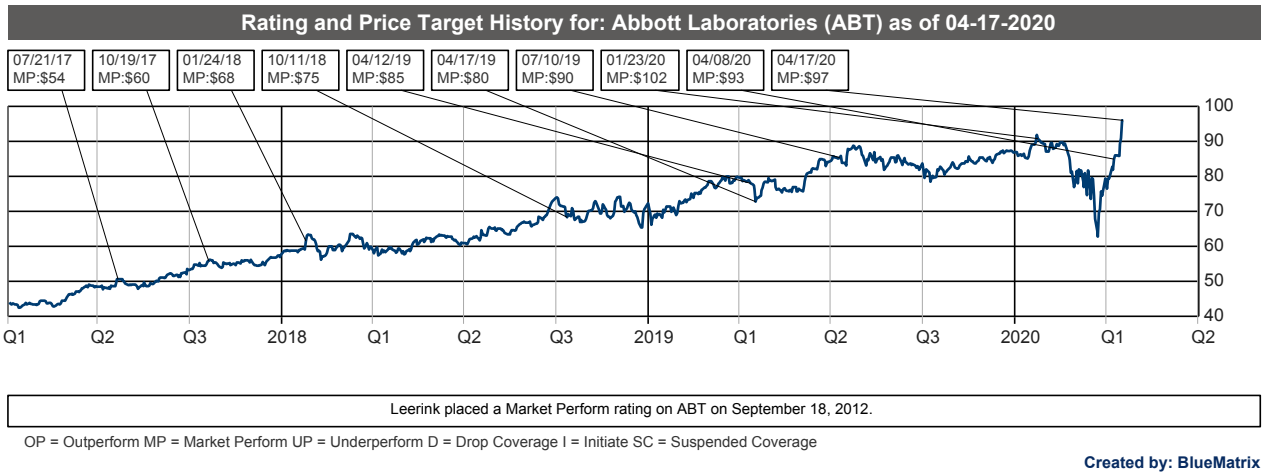
Disclosures Appendix

Analyst Certification

I, Puneet Souda, certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.

I, Geoffrey C. Porges, MBBS, certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.



Valuation

We expect ABT shares to trade to $97, which is the average of our DCF valuations and P/E multiple analyses on 2021 estimates. From a P/E perspective, we applied current 27x P/E multiple on updated 2020 EPS estimates to our new 2021 EPS estimates of $3.60, and arrive a valuation at ~$97. This is further supplemented by our DCF valuation of $91, which is derived from new estimates based on COVID-19 scenario analysis.

Risks to Valuation

Risks include: (1) potential for slowing end-market growth and/or increasing competition for major products; (2) product recalls or manufacturing warning letters that could push operating costs higher and hinder sales growth; (3) successful pipeline execution, which will be key to Abbott's growth story and product approvability, and timing of approvals has become increasingly uncertain in today’s challenging regulatory environment; (4) successful execution on margin expansion opportunities in an environment of increasing price pressure; and (5) potential acquisitions that could be dilutive to shareholders.

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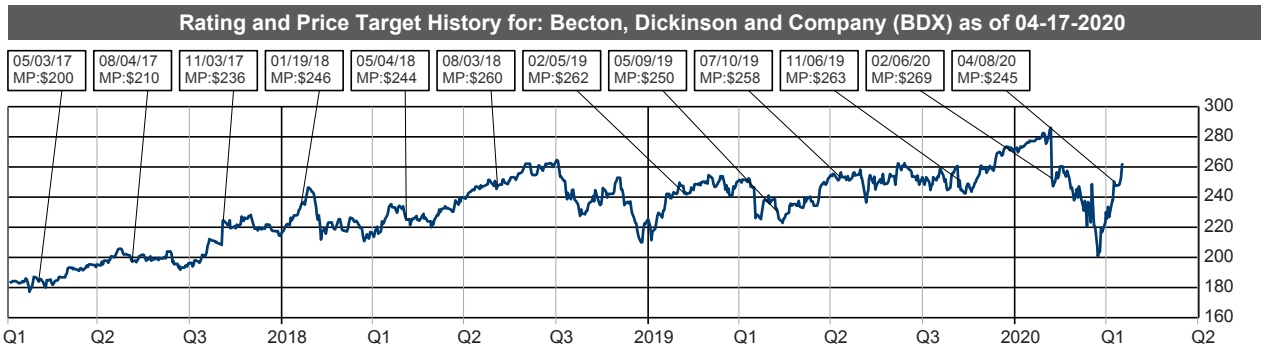

Valuation

Our 12-month PT on BDX is ~$245. We compare BDX to our "adj." S&P 500 1-yr forward multiple estimate of 17.3x (i.e., adjusted for lower earnings), which is ~7% higher than the index's actual 4-week avg. 16.2x P/E avg. We think BDX will prove to be a longer-term MSD rev & 10%+ EPS grower, our PT assumes a 10% premium will hold over the NTM as BDX should have potential to remain a (normalized post-COVID) MSD rev & DD EPS grower. Our $245 PT applies a ~19x (~7% premium) to our $12.87 FY21E EPS.

Risks to Valuation

Risks to our valuation include: (1) if accretion estimates for BCR prove to be overly conservative or aggressive; (2) FX volatility; (3) significant exposure to Emerging Markets, where rev growth can be volatile; and (4) if there is slower-than-anticipated uptake of the company's Diagnostic and Biosciences products.

Distribution of Ratings/Investment Banking Services (IB) as of 03/31/20

			IB Serv./Past 12 Mos.	
Rating	**Count**	**Percent**	**Count**	**Percent**
BUY [OP]	148	73.27	55	37.16
HOLD [MP]	54	26.73	4	7.41
SELL [UP]	0	0.00	0	0.00

Explanation of Ratings

Outperform (Buy): **We expect this stock to outperform its benchmark over the next 12 months.**

Market Perform (Hold/Neutral): **We expect this stock to perform in line with its benchmark over the next 12 months.**

Underperform (Sell): **We expect this stock to underperform its benchmark over the next 12 months.**

The degree of outperformance or underperformance required to warrant an Outperform or an Underperform rating should be commensurate with the risk profile of the company.

For the purposes of these definitions the relevant benchmark will be the S&P 600® Health Care Index for issuers with a market capitalization of less than $2 billion and the S&P 500® Health Care Index for issuers with a market capitalization over $2 billion.

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