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This annual research report seeks to highlight the technological breakthroughs evolving today and creating the potential for super-exponential growth tomorrow.
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Hi, everybody.
My name is Simon Barnett.
I am ARC's Director of Life Sciences Research.
And today, I'm excited to talk about one section of our Big Ideas 2023 presentation.
Today we're going to be focusing on molecular diagnostics.
And before we get into that, I'm just going to show some brief disclosures.
There are certainly risks associated with investing in innovation.
You can see a handful of them highlighted here.
So all right, let's dive in.
Molecular cancer diagnostics.
So today, we're going to be talking a lot about oncology or cancer care.
And specifically, we're going to be talking about the testing and the diagnostics portion of that.
So not as much about therapeutics and medicines, much more on testing.
And on a very high level, we're going to be talking about how the same sorts of blood tests and things that you would typically encounter in the health care system are changing very rapidly, how they're getting cheaper, less invasive, more performant, more accurate, and really changing the way that oncologists treat and manage cancer.
Really speaking, the way we think about this problem is we're using machinery like next-gen sequencing, which we talk about a lot, to take biological signals, molecules that are floating around in your bloodstream and digitizing that and transforming them into digital signals that we can apply all sorts of AI tools to.
In fact, we're going to be talking a lot about something called a liquid biopsy in this section, which is essentially taking a routine blood draw, applying sequencing and AI to really change the way that we can detect cancer and manage it and pick the best treatments.
And we'll end by discussing a little bit about the investable opportunity.

But to jump ahead and just maybe highlight a few numbers, we think that the addressable market for molecular cancer testing just in the U.S. is close to about 95 billion and growing at a rate about 20% annually.
So it's about $5 billion today, growing at about that rate, we think over the course of the entire decade to something in the ballpark of about $24 billion in revenue by 2030.
So there's still even then a lot of headroom to go.
And we think that the enterprise value associated with the companies that are driving this change will expand roughly at a similar rate, about 20% or more per year.
And it's a really timely thing to talk about.
If we zoom out and think about public health and how it's changed over the past century or so, we can see that the age-adjusted mortality rate for things like cardiovascular disease have declined tremendously.
Since 1990, we estimate more than 50% thinking about things like cardiovascular disease, coronary heart disease, and stroke collectively have declined quite a bit.
We've not seen the same thing for cancer in the U.S., roughly about 20%.
So we think that over the next 50 years or so, we're going to see another tremendous improvement in cancer care.
And specifically in terms of that metric, I just outlined cancer mortality.
And some of this definitely is going to be driven by improved therapeutics, so better medicines.
But a big part of it too, which we'll talk about, is actually because our diagnostics and our ability to detect cancer earlier, when it's more treatable, are improving rapidly.
And again, I want to just underscore the urgency of this topic.
COVID-19 over the past few years has really decimated the practice of oncology globally.
We estimate that over the past few years, more than 30 million cancer screenings have been missed and 60,000 diagnoses that would have happened didn't because of the fact that COVID caused a lot of lab closures, made it very difficult for cancer patients to continue on with their treatments or oncology visits.
And that's something that I think is really important to focus on now as we move away from the worst parts of the pandemic.
So starting with this idea of combining diagnostics and therapeutics together, if you take a look at this chart on the left, this is one of the things that we're going to be focusing on today is screening.
So for those of you who may not know, typically when cancer is diagnosed, we can put it into a few different buckets, so distant or metastatic disease, meaning that it's spread through other parts of the body beyond where the cancer originated.
Those diseases are typically very difficult to treat, if not impossible.
You have a regional disease, which is mostly confined and then localized disease, which is just confined to the organ that the cancer originated in.
And so if you look at this chart, what you can see is this interesting trend where roughly only 17% of new cases per year fall into that more lethal, distant or metastatic category.
But that 17% of new cases actually causes more than half of deaths over five years.
And the takeaway of this is just that the importance of early detection is pretty clear.
The more that we can take disease that would have been found later and shift it earlier

in its life cycle to something like regional or local disease, we're giving our therapeutics a better chance to be successful.
We are increasing the possibility of operating with surgery, whereas it might not be possible in the metastatic case.
So these are some of the things that we see when we are able to detect disease earlier.
In addition to that, we hear the phrase precision therapy a lot.
Usually this just means using therapeutics that are targeted towards specific drivers of cancer, like DNA mutations, for example, instead of just one size fits all treatment.
And the interesting, I think, interplay is that diagnostics are actually a prerequisite for precision therapies.
In order to target a drug, we have to identify that target.
And that's what molecular diagnostics are for.
So these tests surface tumor mutations that are unique to a patient and even unique to the tumor, and that helps oncologists figure out what drugs to use and what dose and figure out the best course of treatment.
And you can see since the year 2000, the number of clinical trials that have actually included what's called a biomarker, which is a signal that a diagnostic test can help surface.
That fraction has increased actually pretty substantially.
You can see that down here.
The portion of trials that now include at least one biomarker has actually become more than half.
So more than half of clinical trials started today that are evaluating cancer drugs include at least one molecular biomarker.
There are a lot of different types of cancer testing, and we're not going to cover all of them today.
But I think that when you start to consider the different types of testing that are available to us, one of the best ways to segment this market and get a bearing for where these different tests fit, what their use case is, and this will help us figure out at the very end what the market is, one of the ways that we've conceptualized it internally and I think is pretty intuitive is this plot down here.
So this is not drawn to scale.
It's not representative of any data set.
It's merely meant to be something that's helpful and illustrative of what I'm about to talk about.
So on the bottom you have time going from early adolescence all the way out to late in life, and then on the y-axis you have what's called tumor burden.
So tumor burden, roughly speaking, is essentially the amount of what's called circulating tumor DNA in the body.
So when cancer is growing somewhere, say it's liver cancer for example, it's shedding small pieces of cancer derived DNA into the bloodstream.
So the bigger that the tumor is, the more circulating tumor DNA is in the blood, and we can quantify that amount and use that as a way to assess the burden of disease, how advanced it is.
So the higher it goes, the more advanced cancer is, and the lower it goes to zero, there's

no cancer.
So if you look left to right on this chart here, what you can see is you have different types of cancer testing.
So you have hereditary disease testing, which is trying to figure out, okay, how likely is a person to develop cancer over the course of their lifetime because of their inherited genetics, right?
So some of us are more predisposed and some less.
You have cancer screening, which includes tests like Colagard, for example, which are designed to detect disease early, and I mentioned the importance of that just a couple slides ago.
You also have something called prognostics, right?
So this is right, you know, during treatment or right before, oftentimes a clinician will order one of these tests to figure out how aggressive is the disease, right?
Because we want to be able to adjust and tune the aggression of therapy to match the aggression of disease.
So that's what a prognostic test is.
A newer category that we're going to talk about a lot is called MRD, or Minimal Residual Disease Testing.
Essentially what that means is after you get a cycle of therapy, we use blood-based testing to figure out is this patient responding?
Are they recurring, right?
Is there a relapse later on down the road?
And then finally, for more advanced diseases on the right, you have therapy selection, and this is for patients that have, you know, again, a more advanced form of cancer, and we're trying to figure out what is the appropriate precision therapy or combination of therapies even to treat that patient.
So let's start chronologically talking about screening.
So on the left-hand side, we're going to talk a little bit about, you know, using sequencing to detect mutations early on in the bloodstream and kind of how this field is evolving.
And there's been a really interesting technological trend that I think is important to highlight, and that is that, you know, the most performant tests for screening, the ones that are really good at seeing cancer as early as possible, they're beginning to move beyond just looking at circulating tumor DNA to include other signals of cancer, things like how is the immune system reacting, what proteins are swimming around in the blood that normally wouldn't be there in a healthy patient, right?
So there's genomics, right, that's DNA, proteins are proteomics, right?
So what we're doing is we're combining multiple categories of omics, and that's how you get this title, multi-omics.
And essentially the reason why you'd want to do that is because you can combine these various signals and use AI to actually put them together and make something that's more than the sum of its parts, right?
Make a signal that is loud, it's screaming as soon as you have a very early stage disease.
And the reason for that is because no matter how accurate or how deeply you sequence a blood sample, sometimes those molecules just aren't there, right?

The cancer isn't big enough to shed enough tumor DNA, and that's what you see in this chart here is kind of diminishing returns, right?
So on the x-axis you have an improvement in sequencing accuracy, and on the y-axis you have tumor diameter, so in centimeters how big a tumor is, and you can see this plateau that clearly illustrates that at some point DNA is just not enough.
We have to go beyond that, we have to incorporate multi-omics, and that's what we're seeing from some of the best tests in the field right now.
On the right-hand side we talk a little bit about a specific example, so lung cancer screening.
Lung cancer is one of the most prevalent and lethal diseases, oftentimes it's found too late.
Currently the standard of care is using what's called low-dose CT scanning or medical imaging to screen people that are smokers or may be at other high risk or may have high risk indicators.
The challenge with this is that very few people actually adhere to those guidelines.
Blood-based testing is generally much more adhered to than medical imaging, and so this is some modeling work we did that showed that incorporating the current best version of a lung cancer blood-based screening test on top of, right, so not a replacement, but on top of low-dose CT scanning can actually really improve, and in this case actually increase by six-fold the number of early-stage lung cancers that we can detect per year with the combination versus just, you know, CT scanning only.
And more importantly than that, because it detects so many more cancers than the current standard of care, it actually lowers the cost, the average cost, to detect a lung cancer versus, you know, what the current standard of care would be.
So that's some of the exciting things that are happening in screening right now.
If I go further to talk a little bit about, I think, one of the most exciting categories of screening, it's called multi-cancer earlier detection, and that's a little different than what I was just talking about with lung cancer, because multi-cancer tests are looking for, well, just that.
Sometimes as many as 50 cancers from a single blood draw instead of just one, and this is a really new paradigm that only became feasible recently.
So if you take a look at the left-hand chart, this is some cost sensitivity work that we did, and the main takeaway here on the left is that, you know, if we use what the typical standard is for reimbursement, about $50,000 per life year per patient.
So that's the horizontal dotted line.
You have to be below that to be reimbursed in many cases by the medical system.
And so a multi-cancer test, given current performance and how much cost it extracts from the system versus how much it takes to fund the type of test, at $2,000, it's not reimbursable for anybody.
There's zero market for a $2,000 multi-cancer test.
At about $500, though, things start to get interesting.
Based on our understanding, we believe that a $500 multi-cancer test with good performance could actually be reimbursed.
You can see where it intercepts at about age 45 for people that are older than 45, which is roughly in line with the current age that the American Cancer Society recommends screening.
So we think we're really close to the point where, you know, at $500, there could be a

market and it could be huge.
And on the cost side of that equation, right, so we just talked about price, on the cost side, this is the really important thing to point out is that over the past few years, we believe the cost to actually run one of these tests at scale has been declining more than 90% over the past five years.
So, you know, it's important that that cost is underneath that reimbursement ceiling, otherwise there's no margin, there's no reason for companies to get involved and start selling these tests.
And that's what we're seeing now.
From 2016 down to 2022, that cost has fallen a lot.
And we're at this interesting point where I think instead of trying to, you know, drop that price to the floor, what we're seeing is companies are actually getting and building more efficient tests where the performance gets better, even though costs are kind of leveling out for them.
And the reason why that's important is because better tests that can detect cancer, you know, a lot earlier that have fewer false positives, that's great for making sure that we don't create a lot of cost into the medical system by, you know, trying to treat cancers that aren't there and things like that.
So we think costs will continue to decline.
It's still probably going to take seven or eight years, we think, for multi-cancer earlier detection to really take off.
A lot of that is because of regulatory hurdles and, you know, how long it takes to generate clinical evidence.
But we still think multi-cancer earlier detection can be one of the most powerful tools in an oncologist's arsenal this decade.
Okay, let's talk about minimal residual disease testing, which I mentioned at the beginning.
You know, currently, and for many years, we've used MRD testing for liquid cancers like leukemia, but solid cancers, which comprise roughly 90% of annual diagnoses, have been very expensive to do with sequencing historically.
Most of that is because solid cancers just don't put off a lot of signal into the blood stream the same way liquid cancers do.
So it's not only been until recently that we've been really able to do this, which is to do deep, you know, sequencing of blood to make sure that a patient is responding to therapy.
And what you can see on the chart on the left is actually a combination from several clinical trials across multiple different types of cancer.
And this is a, you know, a controlled study where essentially you can see that at, you know, months since randomization.
So since the beginning of the trial, you see two curves, people that are testing positive for circulating tumor DNA in the blood and those that are negative, right?
And you can see a big gap between those two.
And what that means is that, you know, being positive for CT DNA is actually a really good predictor of whether or not you're likely to relapse, right?
So people that are continually testing negative are likely not going to relapse.

The people that are testing positive, more likely to relapse.
So it's a way that, again, oncologists can get a new field of view that in many cases, you know, is actually more outperformant than something like medical imaging that you can do, you know, quarterly.
On the right-hand side, these are recent trial results that are really exciting.
We had two different randomized controlled arms here.
One that was guided with blood-based MRD testing and one that was not.
And the headline here is that the survival between these two groups was roughly the same, you know, 92 to 94 percent people with relapse-free survival after two years.
But in this case, the folks that were treated with CT, or used CT DNA testing instead of imaging actually were spared chemotherapy.
It was about a 50 percent reduction in the amount of chemotherapy given to that arm, which is great in terms of, you know, cost, but also the morbidity associated with having to be treated with chemotherapy.
Moving on, you know, MRD testing is still evolving rapidly.
One of the big challenges currently facing the field, and you can see this illustrated on the left, is that after very successful surgeries, especially with certain cancer types like breast cancer and prostate cancer that don't give off a lot of CT DNA in the blood, MRD tests can yield false negatives, meaning that cancer is actually still there and potentially growing again.
But our tests are just not sensitive enough to catch it.
They don't have the accuracy to go deep, deep down and detect the earliest emergence.
They're still pretty good, but not quite where we'd want them to be, you know, as a standard of care in perpetuity.
On the right-hand side, you can see how these tests are evolving.
So some of these newer tests are looking at many thousands of different cancer mutations instead of just a couple.
And this has been always a trade-off between performance and cost, right?
But as costs are coming down, which they are again for sequencing, many of these tests are converging on this breadth-over-depth approach, where they're looking at thousands of mutations at the same time.
And that helps them get sensitivity that is as much as an order of magnitude greater.
And that's really important for detecting cancer, you know, after treatment as early as possible, right?
So having more lead time over the current standard of care.
So this is the direction we think the world is going to go here.
More mutations, deeper sequencing, better performance.
And the costs are now there that it's beginning to make sense.
Typically therapy selection.
So again, this is for people that have been more advanced cancers.
Therapy selection has been around a little bit longer than other types of testing that I just went through.
But it's still evolving, and there are still a lot of reasons to get excited about growth in that space.

So I'm going to give just a few examples, and then we'll conclude with sizing the market.
So the first thing to talk about.
Typically therapy selection has been done with tissue, right?
So you take a tissue biopsy, you sequence that cancer sample, and you get biomarkers, you get mutational information that you can use to select the best course of treatment.
Now there are going to be some people, as you can see on the left here, passing filter, failing filter, right?
So there's some fraction of people that do not have sufficient high quality tumor tissue, right?
Maybe they're too sick to get a surgery, or maybe it's very difficult to access that tissue.
For whatever reason, these people are not going to be served by tissue-based testing.
Recently, with new technology, we've been able to develop blood-based versions of therapy selection tests, some of which that got FDA approved just in the past couple of years.
And this is great because what it means is we can rescue some of those people that fell below the filter and actually give them an opportunity to get matched to a therapy where otherwise it would not have been possible with the tissue-based test.
In addition to that, comprehensive therapy selection tests are getting more content, right?
So we're adding more content to them.
We're looking at more genes, we're looking at more mutations.
And what that means is, or what it translates to, is that a greater fraction of patients get the opportunity to have an actionable biomarker extracted from their tumor.
Or maybe it means that some of them can be put on a clinical trial, whereas otherwise we wouldn't have been able to do that.
And you can see that here as you go from a small panel of genes to a comprehensive hundreds of genes, the fraction of people that find or get an actionable biomarker or get clinical trial eligibility, in this case almost doubles.
The last thing I want to mention, again, going back to this concept of multi-omics, right?
Going beyond just the genome to include other categories like proteomics, or in this case we're going to talk about RNA, which is called transcriptomics.
So what we've been starting to do with these newer therapy selection tests is looking at both categories, DNA and RNA.
And when you sequence RNA, in addition, you're much more likely to find what are called fusions.
And fusions are a class of druggable target that some of our best precision medicines go after.
So by doing RNA sequencing, in addition to DNA alone, we detect 29%, almost 30% more fusion targets that we can use to help match people, again, to better therapies.
So multi-omics, multi-modality is definitely a trend that we're seeing with advanced cancer testing as well.
So to conclude on sizing the opportunity, you know, we walked through a lot of different types of cancer testing today.
We talked about, you know, we talked about screening, we talked about MRD testing, and we ended with talking about therapy selection.

We didn't get into hereditary cancer or prognostics as much, but they're definitely included in this calculation and still growing.
So to reiterate the numbers I said at the beginning, we think the total addressable market for cancer testing diagnostics in the U.S. is about $95 billion, you know, only about $5 billion of revenues being generated today.
So it's, you know, vastly under-penetrated.
At the current growth rate, which we estimate to be north of 20% per year, we think that by the end of the decade, that revenue will grow to $24 billion.
Still, you know, a lot of room to go to get to $95 billion.
You can see a breakdown on the right of some of the different categories.
You know, we think cancer screening and MRD are going to be disproportionately large contributors to that revenue opportunity, and that's just because, look, multi-cancer screening as well as, you know, targeted screening for lung, colorectal, and other forms of cancer we think are really going to, you know, explode over the next market cycle or two as we finish out the decade.
MRD testing, again, another really large market that we think is well-served by sequencing-based technologies.
But all in all, that is the revenue estimate that we've given for cancer testing.
And so I'll just conclude by saying that, look, you know, I think this is one of the most exciting areas, certainly for us as a life science team, to really focus on, you know, we've got people focused on the diagnostics and the therapeutics as well and the way that they work together in tandem to fight some of our biggest, you know, drains, not only on public health, but also the economy, is really exciting.
So I'm eager for you to hear Allie Ehrman, she is working on our life sciences team.
She did a great section focused on the therapeutics side, so make sure to take a listen to that.
And I think it's a tremendous piece of work.
So thanks very much.