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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.
We believe that innovation is taking off now, corroborating our original research and boosting our confidence that our strategies are on the right side of change.
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Hi, I'm Ali Ehrman, analyst at ARC Invest.
At ARC, I cover all of therapeutics, including immunotherapies, novel therapeutics, and we also have a heavy emphasis on gene editing, gene therapy, and stem cell therapeutics.
I'm very pleased to present to you the Big Ideas 2023 Precision Therapy section.
A few just cautionary tales of risks on investing in innovation.
One is the rapid pace of change.
So as we know, new therapeutic modalities are invented every day and at a quicker and quicker pace.
We also know that there are uncertainty and unknowns with these new modalities as they come into patients.
We need to be careful and we need to ensure that we get regulatory hurdles that are overcome such as with the FDA and other governing bodies.
There's also exposure across sectors and market cap in addition to political and legal ideas and issues that may come up over time.
However, we believe that these innovative therapies are and potentially can change the world.
And so we're very excited to talk about the innovations here.
So precision therapies are especially exciting because we believe that they're going to expand medicine and be able to potentially treat and cure disease.
And so previously we were masking symptoms, whereas now we may be able to actually attack the root cause of disease.
So with precision therapies, they are patient centrics.
So they focus on a patient and more and more therapeutics are becoming individualized as well.
So we are a particular patient.
We also, as I mentioned, target the root cause of disease, not just masking the symptoms

and potentially even cure the disease.
And so we're not going to continue with a chronic therapy, but rather one dose of a potential cure.
They're designed using novel experimental and computational methods such as AI and potentially neural network-based algorithms in which we can predict protein folding like Alpha fold, Rosetta fold, and so many others.
And these precision therapies could be then developed faster and actually more cost effectively than traditional therapies, as you'll see throughout this presentation.
Rapid advances in technologies like artificial intelligence, which isn't, for example, an example I just gave on neural network-based algorithms, DNA RNA sequencing, which Simon Barnett will talk more about, CRISPR gene editing, and other novel therapeutics, and also laboratory automation really have spawned these new therapies.
What they'll do then is they'll enable the treatment of diseases that we previously thought we could never find a cure or even a treatment for.
So really the most exciting thing though is that precision therapies are becoming multi-omic.
What we mean by that is that there are multi-datasets that we can use in which we can figure out different therapeutics to treat these diseases with, and these are going to have mechanism of action spanning the DNA, RNA, proteins, and even more.
Based on ARCS research though, the enterprise value of companies focused on these precision therapies could then appreciate 29% at an annual rate from about $500 billion in 2022 to about $3 billion by 2030.
Pharmaceuticals really needed innovation.
As you can see on the chart on the left hand side, unlike the last about 30 years, the change in death rates associated with cancer and cardiovascular diseases during the past five years, it has not drastically improved.
As you can see on the x-axis we have the years, on the y-axis the percent change in death.
This is per 100,000 people, and we see cardiovascular cancer and neurological in the annual percent change, and these are death rates by disease area.
As you can see, this suggests that existing approaches have really reached this plateau or reached this area in which we have diminishing returns.
Emerging precision therapy modalities could become best in class, and they could in turn lower the death rates across many diseases, including neurological, as you can see on the right and left hand side below.
If we take an example like DNA, we can see that for DNA we would have CRISPR, we would have cas enzymes, we would have base and prime editing.
An example there could be a drug that vertex and CRISPR therapeutics are working on for beta thalassemia and sickle cell disease, and for that disease it would be a one-time treatment, and they are close to commercialization with having their BLA submission on a rolling basis currently.
But we're also looking at older pharmaceuticals.
These innovative precision therapies have certain advantages, and we think that these could cause significant shifts in market share.
Precision therapy toolkits are broadening with techniques that target the DNA, like the example I gave for the CRISPR cas, the base, and also for prime editing, the newer

versions.
Also for RNA, so RNA editings like for ASOs and other modalities, so ASOs, for example, can block the RNA from producing proteins.
So for example, in a tersin, is a therapy used for variant and wild type form of TTR, and it works by degrading the TTR messenger RNA and not allowing the RNA to make any more of that protein.
When it's not treated, TTR polyneuropathy can lead to a buildup of proteins in the nerves, because you would be overproducing this TTR, a transthyroid protein, and an ASO could block that production.
If there's no intervention, then you may experience numbness or tingling, and then there's another form of TTR called cardiomyopathy when the buildup is actually in your heart, and you may experience heart enlargement and other irregularities.
If we talk about proteins, we can think about targeted protein degradation or TPDs.
So targeted protein degradation or TPDs, they basically cause proteins that are, or they will target disease-causing proteins, and why they'll do that is they'll harness the body's own mechanisms.
So for example, we have a waste management system for proteins, and that's why the whole body can use to target the disease-causing proteins using small molecules.
And then obviously there are other modalities, but all of those funnel into innovative precision therapies, and we assume that there will be certain advantages, including fewer off-target effects, more preselection biomarkers, better safety profiles, faster development timelines, and essentially more treatments for rare diseases, which is one of the most important.
And with all of that, we assume that there will likely be an increased likelihood of approval as well.
This all funnels into the central dogma.
So the central dogma, what it does is it describes the flow of information through biological systems.
So we have DNA as the template, and you can see it on the left-hand side in this depiction, and then our cells will transcribe RNA molecules, and then those will translate into proteins.
So DNA mutations, what essentially happens is they can still follow the same process of DNA to RNA to protein, but what they'll do is they'll produce dysfunctional proteins at the end of it, and proteins are really the main cause of disease, but you can actually target any molecule, so the DNA, RNA, or protein, with the precision therapies that we'll talk about in this stack.
So we believe that more therapeutic targets could result in better health outcomes for patients, so we'd love to see further innovation and further targeting of new pathways and creating better therapeutics for patients.
So when we think about innovative therapies, they're really targeting each part of the central dogma, which we just explained, the DNA, RNA to protein.
So researchers can target DNA, and the example we're giving here is using gene editing to potentially cure or prevent heart disease and lower LDL.
They can silence RNA, and this example we're talking about Patissaran, which was a drug developed by El Nilem, and that's to control polyneuropathy, which is the example we gave earlier, and then they can degrade proteins to limit the growth of tumors.

So just for a little bit more context in those.
For DNA, this modality is Verb 101, and it uses an mRNA and a guide RNA in an LMP mediated delivery, and then it goes to target the liver.
The company specifically is using base editing technology, and they make a single change to a misspelling in the genome.
So in this case, they're correcting an A to G change at the PCSK9 gene, and what they're doing is they're doing that to disrupt the production of PCSK9 protein, and therefore lowering LDL or bad cholesterol.
The company actually presented some in vivo data, which is showed here.
This is in non-human primates, and it's typically, that's the largest animal that's most closely related to humans that we study really before going into a human study, and they found that the drug achieved about an 89% reduction in blood levels of the PCSK9 protein at two weeks after baseline.
So this therapy is currently in the clinic, and we anticipate further details and data to hear on really its efficacy and durability.
For the RNA silencing example, so we talked about this one a bit previously, but this is the TTR polyneuropathy that we discussed.
It's a drug that is currently approved by El Nilem.
Many others are also working on drugs for this indication, including Ionis with an ASO, and also in teletherapeutics with a gene edit.
So here you can see that the percent change in severity from Patissaran is significantly better than that of placebo, and hence why it's approved.
It's also worth noting that while it is approved for polyneuropathy, it is also being evaluated for cardiomyopathy, but has not been approved yet, and cardiomyopathy is that indication where we talked about the significant buildup of the TTR protein in the heart.
Last but not least would be TPDs, so targeted protein degraders.
They have not been approved to date, but there are several trials going on, and we'll talk about that a little bit more later in the presentation, and they're also being tested in combination.
So here is an example of a drug that was developed by Nurex.
It's being tested on B cell malignancies, and they, for this particular trial, they've received at least two prior systemic therapies, and as you can see when compared to standard of care, it appears that a TPD may be superior, or using a TPD in combination with a novel cell therapy that we have seen some efficacy with in the past.
So gene editing is pretty close to commercialization, so we're going to focus on DNA for this section.
So what is gene editing?
Well it's the ability to modify, insert, or delete genes that could stop disease at its source.
So just like we talked about before, this is really to start moving things upstream.
So creating a society in which we focus on actually targeting the root cause of disease instead of just allowing or keeping symptoms at bay.
Gene editing based therapies are in the clinic.
If you look at the chart on the right, I mean the top chart, you can see on the y-axis we have the number of active trials.

On the x-axis, the different diseases and indications that they're in.
And as you can see, it really goes through a wide range of diseases, including things like rare disease, which seem to be the highest, which makes sense, but also musculoskeletal, immunology, and dermatology, a few trials there.
You can also see that there's differentiation here between the ex vivo trials and the in vivo trials.
So it's worth reminding ourselves what is ex vivo.
So ex vivo gene editing is an approach where you're modifying a patient's cells outside of the body, and then you're transplanting them back inside of the body.
And for some diseases, that's going to be sufficient.
An example of a disease there would be like beta thalassemia and sickle cell disease, which we talked about at the beginning.
But you may need for some diseases an in vivo approach.
And an in vivo approach is one where we modify a patient's cells inside the body as opposed to the ex vivo approach, which is modifying them outside of the body and then transplanting them inside the body.
As you can imagine, this is easier in a number of different ways, one from a manufacturing and scaling perspective.
It also expands access to a greater number of indications like liver, eye, central nervous system, and muscles.
If we look at the chart on the bottom, you can see years on the ex access.
And then on the Y, we can see number of active trials using gene editing.
That is represented by the bars.
And then we predict what will happen after 2023.
So those are sort of the non-filled in bars.
And then the dotted line on the chart shows the projected number of gene editing product approvals.
And as you can see, it looks like gene editing clinical trials could triple by the end of the decade.
And that would really accelerate the first product approvals because the more trials we have, the more likely a product approval would be.
Moving on to thinking about sort of commercialization, right?
So as we get closer and closer to commercialization, how do we think about that?
And so gene editing therapies could command about a median price of about $2.5 million.
And it could be much more for certain indications.
So an example that we have about that is there was a recently approved gene therapy for hemophilia B, which costs about $3.5 million per dose.
But that could make sense if you look at the lifetime direct costs of treatment for these hereditary diseases.
So if you look at the chart on the left-hand side, you can see a few different diseases.
So sickle cell, the direct costs would be about 1.3.
And then it goes up from there, just a few examples.
So sickle cell diseases, when you inherit two mutated hemoglobin genes from your parents, then you get the abnormal hemoglobin, which can cause your red blood cells to get in that

half-moon sort of sickle shape.
It also becomes rigid, and that can block the flow of blood and oxygen to your organs.
And we see that the direct costs to sickle cell, while one of the lowest in the charts, are still quite expensive.
HAE will create extreme swelling to the body, the face, the limbs, and sometimes, and dangerously, obviously, the airway.
Then we have hemophilia, as an example, which is a blood clotting disorder.
That's where you don't produce enough blood clotting proteins, and this can obviously be very dangerous, because if you have an accident and you're bleeding, you could have trouble clotting, and you could bleed for longer than the average.
Mucopolysaccharidosis type 2 can also be called Hunter syndrome.
That's a rare inherited disease, and it happens when a person is missing or just doesn't have enough of an enzyme that is used and very important in the breaking down of chains of sugar.
Some symptoms for this disease could include respiratory tract infections, vulver heart disease, hearing loss, etc.
And these disease, obviously, as we talk about them and explain them and understand their symptoms, have many direct and indirect costs.
They also have quality of life issues that we need to think about, and obviously mental health issues as well.
However, if you look at the direct costs, obviously, hemophilia being one of the largest at 28, but very expensive, but also very per indication, which is why we say that there would be a median price, but could really vary based on the different indications.
And then if you look at the chart on the right-hand side, years on the X axis, and then obviously we have gene editing, annual revenue in billions on the Y axis, and you can see we have a base and a high case for our gene editing revenue projections.
And as you can see here, we think it could be about 30 billion, and that will really depend on approvals for different diseases, which companies are looking to create therapeutics for right now.
So for example, type 1 diabetes obviously affects a vast, vast number of people.
And so if certain indications are approved by that time, which is probably around when they'll go to the FDA, then we could scale that category up to about 60 billion by 2030.
Now moving on from DNA-based therapeutics to RNA-based therapeutics, we think that they're really gaining traction.
So RNA-based medicines really alter the structure, function, quantity, or localization of RNA and other molecules.
So this class of medicine can really treat the undruggable targets, which is something that's very exciting, especially for rare diseases.
So small molecule therapies target the active binding site of a protein.
Only 14% of proteins have those sites, so RNA-based medicines could really help close that gap and could potentially treat more indications.
So then if you look at the chart on the left-hand side, the number of patents granted over time is obviously significantly improving.
So during the past 20 years, the number of annual RNA patent grants has increased about

10-fold, and we see that trend continuing to emerge.
We also see that the number of RNA-based therapies that are in clinical trial pipelines has been quintupled.
That's going to be to about 500, and you can see on the chart on the right, on the y-axis, we have the RNA-based therapy by clinical trial stage, and you can see in the very light blue that's preclinical trials, so before in humans, and then phase one, two, and three in green, black, and beige, or mauve.
And you can see here that the preclinical trials are really accelerating, which means in sort of the subsequent years, we'll see a large amount of trials, which will go into the inhuman phases of phase one, two, and three.
RNA-based therapies are exciting for multiple reasons.
When we talked about some of those undruggable potential indications that RNA-based therapeutics could be used for, they're also exciting because they should lower cost and they should improve time to market.
So lowering cost and also lowering the time it takes for clinical development is something that we see with RNA-based therapeutics.
So traditional clinical development costs, including the cost of failures, are about $2 billion, and they take about 10 years.
And that's before you even get to commercialize your product.
But we think that multi-ohmic breakthroughs, like we've talked about earlier in the presentation, and examples that we've given earlier as well, but next generation sequencing, CRISPR gene editing, AI, and others, could potentially allow for timelines to decline because they'll allow for less drug failure rates and they'll allow for quicker commercialization.
So if you look at the chart on the left-hand side, we compare antibody and small molecules, which are sort of the more traditional approaches to an RNA-based approach.
And we look at how long the clinical development takes based on their therapeutic class.
And as you can see here, the production of RNA-based therapeutics is pretty much faster.
So you can see that it takes about including failures.
It averages about five years for RNA-based therapeutics, whereas small molecule and antibody trials have averaged about 10 years.
When we think about the cost of clinical development, we compare any therapeutic modality to an RNA-based therapeutic modality and the y-axis is in millions.
And you can see that RNA-based therapeutics average about $1.25 billion, and then small molecule and antibodies average about $2 billion.
So large cost savings and time savings, which accelerate time to market and reduce failure rates.
Lastly, we're going to talk about target protein degraders and how they can treat many more diseases.
So target protein degraders leverage our body's own system and they'll then lower the number of disease-causing, misolded proteins.
So TPDs have really doubled the number of drug-able proteins, just similar to what we said about RNA as well, and they're in the clinic.
They're in the clinic for a variety of different disease indications, including oncology, auto immune, and fibrotic diseases.

And sometimes they're even in combination with cell therapies that we've seen some efficacy with in the past.
So if you look at the charts on the right-hand side, the TPD patent publication, so we show the first TPD complex crystal structure, and you can see just after that the number of patent publications really sort of takes off.
So during the period of about 2015 to 2020, the number of TPD patent publications really increased about tenfold.
And then if you look at the maturity of the TPD, you can see that the number of TPD and if you look at the maturity of the TPD clinical landscape, which is the chart just under that on the right-hand side, IND, so the Investigational New Drug Application is sort of the preclinical, starting to get clinical application.
And we see very, very large numbers of IND in Phase 1 TPDs, and Phase 2 we have just a few, and then obviously Phase 3, nothing yet and none approved.
But as we can see, that will start to really tailor and go into the Phase 2-3 in subsequent years.
And so we see that there's been about an 88% of TPD trials in the early phases, so as I said, we'll likely see many, many more in Phase 3 in the next five to ten years.
And then if we look at the investment in the targeted protein to greater space in terms of licensing deals, but also capital investment, we see that the number of TPD licensing deals has increased more than about tenfold to about 50-plus, and we see that as continuing to increase.
So TPD therapies could address this undruggable proteome, as we mentioned.
So more than half of protein targets under investigation are TPD enabled, so if you look at that little section that's being covered with a little black hat, targets under investigation that are TPD enabled are the darker blue, and those non-TPD enabled are, I guess, the middle color blue, and we believe that these targeted protein degraders have more than double the number that they can drug for human protein targets.
So one TPD molecule can degrade hundreds of target proteins, that's because they have this iterative mechanism of action, but traditional small molecule inhibitors can really only target one, and that's one of the reasons why TPD is very exciting as a modality.
It's also exciting because they have a very attractive safety profile, and if you look at the chart on the bottom, those are the things that really sets apart the benefits of the TPDs versus the small molecules, and as you can see, small molecules have obviously been approved, but TPD is currently in phase two, and we see approvals coming in subsequent years.
So innovation is really key to the efficiency of research and development.
So on this slide, we want to focus on ARC's view, and then we want to focus or compare it to the more traditional view as well.
So in ARC's view, we believe that innovative precision therapies are undervalued.
We also think that they have a more attractive risk-adjusted net present value, as you can see on the chart on the left-hand side, and we think that's relative to large pharmaceutical companies that really focus on some of these traditional therapeutics like small molecules, but based on our research, the total enterprise value of innovative precision therapy companies should appreciate to about 29% with a compound annual growth rate or a CAGR from about $500

billion in 2022 to $3 trillion by 2030.
If you look at the chart on the left, this shows innovative drugs being offered at a more attractive risk-adjusted NPV, and this is ARC's view.
So you can see the percentage of candidate drugs in pipeline, and its probability of RNPV of sales.
And so in the lighter blue, that's the probability for the innovative drugs.
In the darker blue, that's the probability for the more conventional drugs.
And then we contrast that with sort of the market's view, and we think that the market is ascribing too little value to some of these innovative therapies relative to those older traditional medicines.
So you can see here, this is the market-implied RNPV program in millions, and you can see obviously the large cap small molecule being the largest, innovative kind of being sort of less than that, TPDs even less, and then gene editing being a little bit more than TPD and maybe a little bit more than the innovative aggregate.
That will do it for our precision therapy section today.
We look forward to engaging with comments, questions, and hope to hear more.