Company Participants
Michael Brophy - Chief Financial Officer
Steve Chapman - Chief Executive Officer
Solomon Moshkevich - President, Clinical Diagnostics
Alexey Aleshin - General Manager of Oncology & Chief Medical Officer
John Fesco - President & Chief Business Officer
Conference Call Participants
Subbu Nambi - Guggenheim
Puneet Souda - Leerink Partners
David Westenberg - Piper Sander
Tejas Savant - Morgan Stanley
Doug Schenkel - Wolfe Research
Matt Sykes - Goldman Sachs
Operator
Ladies and gentlemen, thank you for standing by. My name is Desiree, and I will be your conference operator today. At this time, I would like to welcome everyone to the Natera Inc. Fourth Quarter 2023 Earnings Call. All lines have been placed on mute to prevent any background noise. After the speakers' remarks, there will be a question-and-answer session. [Operator Instructions]
I would now like to turn the conference over to Michael Brophy, Chief Financial Officer. Please go ahead.
Michael Brophy
Thanks, operator. Good afternoon. Thank you for joining our conference call to discuss the results of our fourth quarter of 2023. On the line, I'm joined by Steve Chapman, our CEO; Solomon Moshkevich, President, Clinical Diagnostics; and Alexey Aleshin, General Manager of Oncology and Chief Medical Officer. John Fesco, President and Chief Business Officer is also on the line and will be available for Q&A.
Today's conference call is being broadcast live via webcast. We will be referring to a slide presentation that has been posted to investor.natera.com. A replay of the call will also be posted to our IR site as soon as it's available.
Starting on Slide 2, during the course of this conference call, we will make forward-looking statements regarding future events and our anticipated future performance such as our operational and financial outlook and projections, our assumptions for that outlook, market size partnerships, clinical studies and expected results, opportunities and strategies and expectations for various current and future products including product capabilities, expected release dates, reimbursement coverage and related effects on our financial and operating results.
We caution you that such statements reflect our best judgment based on factors currently known to us and that actual events or results could differ materially. Please refer to the documents we file from time to time with the SEC, including our most recent Form 10-K or 10-Q and the Form 8-K filed with today's press release. Those documents identify important risks and other factors that may cause our actual results to differ materially from those contained or suggested by the forward-looking statements.

Forward-looking statements made during the call are being made as of today, February 28, 2024. If this call is replayed or reviewed after today, the information presented during the call may not contain current or accurate information.
Natera disclaims any obligation to update or revise any forward-looking statements. We will provide guidance on today's call, but will not provide any further guidance or updates on our performance during the quarter unless we do so in a public forum. We will quote a number of numerical growth changes as we discuss our financial performance. And unless otherwise noted, each such reference represents a year-on-year comparison.
And now, I'd like to turn the call over to Steve. Steve?

Steve Chapman

Great. Thanks, Mike. Natera is focused on transforming the diagnosis and management of disease worldwide. Our growth is driven by combining our innovative technology with significant peer reviewed clinical evidence that supports the utility of our products. We've had a lot of great news since our presentation at the JPMorgan conference and we're excited to get into the highlights.
We finished Q4 with $311 million of revenue, which was $11 million ahead of the preannouncement we made in January and represents 43% growth over Q4 of 2022. Full year revenues were $1.080 billion an increase of more than 30% compared to 2022.
On volumes, we processed 2,496,000 tests in 2023, which is roughly 6,000 units ahead of the preannouncement. We processed 341,000 oncology tests in 2023, representing year-over-year growth of 73.5% and we also saw strong growth metrics in women's health and organ health.
Gross margins in Q4 came in at 51.4%, compared to our Q1 margin of 39.9%. We finished the full year at 45.5% above the top end of the Q3 guide.
As Mike will cover later in the call, we had some revenue true ups and lab savings in Q4 that don't repeat every quarter. We estimate organic revenues in Q4 were roughly $306 million and gross margins were roughly 49%, which still represents a significant improvement versus previous quarters. And as we discussed at the JPMorgan conference, we also made great progress on cash burn throughout the course of the year, ultimately reducing our cash burn by roughly $193 million in 2023 compared to 2022.
The guidance for 2024 reflects the continued momentum in the business that generated these very strong results in 2023. We are guiding revenues of $1.320 billion to $1.350 billion gross margins of 50% to 53% and cash burn for the full year of $50 million to $75 million. On cash, we estimate we will be cash flow breakeven by Q3 or sooner. What's most impressive is we will be achieving this cash flow breakeven quarter while still making very significant investments into our core business.
You'll see later in the guidance that our investment in research and development and commercial operations remains robust in 2024. This includes major investments in core product enhancements and line extensions, plus potentially guideline enabling clinical trials that we believe could benefit patients in the years to come. We can do this because our core fundamentals are so strong. We're in large expanding markets, our volume is growing rapidly and our margin is expanding with ASP increasing and COGS going down.
I'll now hit a few other highlights before we go into more details on each. First, we think our recent acquisition of Invitae's women's health assets is well timed given the clinical value of

expanded carrier screening and the strong trends we are seeing there and we're feeling positive about our progress on the acquisition thus far.
In organ health, we're building momentum as we complete enrollment and readout major innovative clinical trials. We'll be talking today about some big first of their kind perspective studies in donor derived cell free DNA and how they may positively impact patient care.
Finally, in oncology, earlier this week, we were pleased to announce that the MolDX has expanded coverage for Signatera to neoadjuvant monitoring in breast cancer and separately for MRD and recurrence monitoring in ovarian cancer. We've had a drumbeat of exciting clinical developments across a range of indications including CRC, muscle invasive bladder cancer and breast cancer.
I'm excited for Alex to also talk about the modern study in bladder cancer, which just enrolled its first patient a few weeks ago. Finally, we've had a string of good results on the IP front that I think puts us in an excellent position in 2024 and beyond.
Okay, great. Let's get into details of the results on the next slide. Revenues exceeded our expectations at $311 million driven by continued strong volume growth and excellent ASP traction across the business, particularly in women's health and oncology. We previously had a goal to get oncology ASPs above $1,000 by the end of 2024 and we actually hit that level in Q4 of 2023.
That's great news because we now think we can get a full year's benefit of higher ASPs in 2024 and we think there's still room to drive Signatera clinical ASPs another $50 to $75 higher just by continuing to execute on currently covered indications. Of course, this week's announcement on new Medicare coverage will help us as well.
The commentary on women's health ASPs is broadly similar. We saw encouraging sequential quarterly progress throughout the course of 2023 and preliminary analysis of Q1 trends suggest that we are on track for continued improvement so far in 2024. Volume was a strong driver of Q4 performance as well and you can see the annual volume trend on the next slide. As mentioned earlier, we came in 61,000 units ahead of our preannouncement in January.
I have a separate slide on oncology coming up, so I'll focus on women's health and organ health here where we saw strong growth in the full year 2023. As the year ended, we saw an acceleration of women's health including hitting a record units per receiving day in December. This strong momentum carried into January as well and that was prior to the acquisition of Invitae's women's health assets where we're just now starting to see volume come in.
In organ health, as the year progressed, we saw a return to growth in the donor derived cell free DNA business after the initial pullback in early 2023 due to the coverage changes. We think we're well positioned going forward in donor derived cell free DNA to compete given the significant body of peer reviewed evidence that we generated and the unique features of our tests. Also, we continue to see strong interest in Renasight after the RenaCARE publication. This momentum is great and we're off to a fast start across women's health, organ health and oncology.
On the next slide, we're showing the ramp of our oncology business, which continues to outperform. In Q4, we did 98,000 units, another strong sequential quarter increasing by 9,000 clinical units over Q3 of 2023. For the full year of 2023, the growth rate was 73.5% over 2022. We're continuing to see strong growth across the core indications including colorectal cancer, breast cancer, muscle invasive bladder cancer and immunotherapy monitoring even as we add

new indications. Roughly 40% of oncologists used Signatera in Q4, which shows the strong clinical utility of the test and we have strong momentum going into 2024.
Just as critical as revenue and volume growth is the gross margin traction we are seeing. I think this slide is a good snapshot of the business maturing. Over the course of the year, our ASP and COGS initiatives delivered above our expectations, particularly in Signatera, ASP and COGS, both of which improved over the course of 2023.
As I mentioned at the top of the call, we think the underlying repeatable gross margin in the quarter was roughly 49%. Our 2024 guide implies meaningful continued gross margin improvements based on ASPs and cost drivers that are within our control.
In addition, we've also got a number of potential upside drivers to both revenue and gross margin that we'll discuss later in the call that aren't included in our guide. So the net result of strong revenue growth and expanding margins on stable operating expenses is a dramatic reduction in cash burn we achieved in 2023.
This is essentially in line with the data we released in January. As discussed previously, we accelerated a chunk of 2024 scheduled CapEx in December to take advantage of some large year-end discounts, which has helped us set up for an efficient year in 2024. Two years ago, we set a long-term target to get a cash flow breakeven quarter this year and based on these results plus the early data we are seeing so far in Q1, we are confident that we can reach that milestone by Q3 of this year if not sooner.
Of course, cash flows are dependent in part on payer response times to submitted claims and so are inherently difficult to forecast with precision on a quarterly basis. But the point is that we're continuing to build momentum and our confidence in achieving this goal is stronger than ever.
Finally, I think anyone that follows this space has taken note of our results on the IP front. Since we created the category of tumor informed MRD in 2017, we've had 2 companies attempt to follow us into the space, requiring us to enforce our IP against them. The good news is that they've now both been enjoined for violating our IP. The permanent injunction against Archer and Invitae was ordered after the conclusion of a jury trial and then subsequently a preliminary injunction was entered against NeoGenomics.
One notable point about these results is that different sets of patents and different judges are at issue in each of these cases, which I think demonstrates the strength of the IP estate that protects our core technology. The Natera's IP litigation offers another case in point, which generated a sizable jury verdict for damages based only on past infringement of our patents. The process is still ongoing to determine whether future royalties will be awarded.
And on the Ravgen trial, we were found to not willfully infringe and the damages awarded were obviously much lower than what Ravgen was requesting, but we still respectfully disagree with the outcomes of the trial and we plan to appeal certain of the rulings.
Okay. Now, let me hand it over to Solomon to discuss updates in women's health and organ health. Solomon?

Solomon Moshkevich

Thanks Steve. Let's start with the Invitae deal.
First, recall we secured a judgment on past damages in our Archer IP litigation of roughly $20 million. We anticipated that it could be difficult to collect that amount from Invitae given their financial issues. So we applied that judgment amount as part of the consideration in this deal.

We also paid Invitae $10 million upfront and if we have excellent retention of Invitae's accounts, there's a potential milestone payment that we can make of up to $22.5 million. We would be very happy to make that payment because it would mean that the deal is working extremely well for us.

As a reminder, we did not take on any of Invitae's products, its lab operations, nor its physical assets. We did hire roughly 30 of their women's health sales reps and our goal is to provide a seamless transition of those Invitae accounts to Natera's Panorama and Horizon products. Our team is working hard to retain as much volume as we can and we're doing well.

We expect to retain at least $20 million to $25 million in high quality recurring revenue per year, but we think there is a potential to increase that up to $50 million to $60 million depending on how things go, especially if we see clinical practice guidelines for expanded carrier screening or 22q, which we think could come as soon as this spring and would provide upside to these numbers. So we think the deal rationale is strong and we look forward to providing more updates as the year progresses.

One of the keys to our offering in women's health is our highly differentiated screening test for the 22q microdeletion. As 22q goes into societal guidelines and becomes commonplace as we believe it will, the differentiation that Natera has in its 22q test is going to become increasingly valuable. When we run our test, we're using our core SNP-based technology that allows us to target this very small region of the genome, which is around 2.5 to 3 megabases.

This allows us to get over 25x more observations in this particular region of interest than companies doing massively parallel shotgun sequencing, which creates a significant technical advantage that has translated into excellent clinical performance as demonstrated in the SMART trial.

We think the SMART trial represents the gold standard in clinical validation that would be very hard to repeat. As a reminder, SMART was a 7-year multicenter prospective trial that enrolled more than 20,000 patients and collected genetic outcomes from prenatal specimens and newborn blood spots. In this trial, Panorama demonstrated overall clinical sensitivity of 83% and specificity of 99.95%, which translates to PPV of 52.6% overall and a PPV of 100% in cases with ultrasound anomalies.

As 22q has gotten more attention in the wake of a strong guideline from ACMG and anticipated guidelines from ACOG, we have noticed competitors starting to present datasets with PPV metrics that look high, but with screen positive rates that are low or completely unreported. In one report from a lab doing shotgun sequencing, the screen positive rate was approximately 1 in 6,500, which is 3 or 4 times lower than the expected population incidence, suggesting that they might be missing a significant number of affected pregnancies.

In addition, other labs are making comparative claims based on patient cohorts that had very high rates of ultrasound findings, where we saw PPV of 100% in the SMART trial, as I mentioned previously. In our view, a test is not appropriate for population screening if you don't know the clinical sensitivity and [indiscernible]. These are typical marketing tactics that we've seen before and we do think physicians will see through it.

Moving now into carrier screening, we've seen really strong adoption in the past year and we believe we're the number one ordered next gen sequencing based carrier screening test in the United States. Our mix of broader panels increased after the exit of 704 from the market in late

2022. And we are finding that quite a few of the new transitioning Invitae accounts also have a strong mix of broad panels.
So in addition to our existing portfolio, we are really pleased to be launching a new 613 gene panel and a totally flexible custom panel option to serve these customers. Horizon provides high detection across all genes, including the challenging ones where other labs may struggle. With these new panels together with our investments in variant curation, our genetic counselor team and lab automation, we think Horizon is well positioned to remain a leader in the field. Broad panel carrier screening is also a hot topic for ACOG, where we expect to see an expanded guideline in 2024.
Turning now to organ health, where we are excited about the prospects for 2024 and beyond. We think the strength of our clinical data, our commercial execution and our intellectual property estate enables us to compete for the leadership position in this space. Our clinical data generation in organ health has been prodigious in the last 5 years, where we now have 39 papers published or accepted in top journals.
In the heart indication, we recently had our third paper accepted for publication, the Trifecta Heart Study, which demonstrated strong correlation between Prospera and endomyocardial biopsy assessed with the molecular microscope. Reporting an area under the ROC curve of 0.9. You can see in these 3 high quality data sets on the page the consistent performance across the Trifecta, DTRT and DEDUCE trials, including in adults and pediatrics.
This performance laid the foundation for us to start the randomized controlled ACES trial, which aims to show the non-inferiority of using surveillance with Prospera compared to surveillance biopsies that most centers do on a monthly basis in the first year after a heart transplant. Sites are preparing for their first enrollment this summer.
Now in the kidney transplant space, we have finished enrollment of 3 major trials, proactive, pedal and motor. Our first paper from the proactive study has now been accepted, showing that Prospera can detect active rejection up to 4 months ahead of biopsy. No other cell free DNA lab has lead-time data like this and we think this data might support payer coverage in the surveillance setting. We look forward to this publication and we're already working on additional readouts from this study.
Moving on to the pedal trial with over 500 patients enrolled from 28 different sites, this is an important prospective utility study aiming to show how Prospera can be used serially after a rejection event to predict therapeutic response and outcomes. We believe this study can bring significant value to the field for this important indication.
Finally, the motor study is generating novel clinical validity data showing the performance of Prospera in cases of multi organ transplantation, including kidney heart, kidney pancreas and kidney liver. We expect these key trials to extend our data leadership in a meaningful way, so we're excited about 2024.
Moving now to oncology. Signatera continues to benefit from a significant first mover advantage across multiple areas. The first is our significant leadership in technology and innovation, as exemplified by our strong IP portfolio and two recent favorable injunction decisions. We continue to invest in new innovation projects with multiple MRD related products that we plan to launch in 2024 and 2025. We also continue to invest in expanding our market leading clinical portfolio.

Now with 70 peer reviewed oncology publications to date and multiple prospective randomized trials ongoing, many of which were designed several years ago, we believe this pipeline will continue generating data over the coming years that can become practice changing. In market access and reimbursement, today Signatera test is covered by Medicare and a growing number of private payers in colorectal cancer, bladder cancer, breast cancer and pan cancer eye immunotherapy monitoring. We have now added ovarian cancer to that list, which Alex will cover in greater detail in a moment. This broad coverage allows oncologists to use Signatera across the majority of their patients.

Finally, I want to highlight the operational capabilities that we've developed over nearly half a decade of experience. I believe many in the field discount the complexity of delivering tumor informed and personalized MRD results back to physicians and patients in a timely manner and at scale. There is a real experience curve here, which is not easy to replicate.

We continue to expand and refine these capabilities through improvements to the turnaround time, expansion of our mobile phlebotomy services, integration into electronic medical records, and the launch of industry leading digital solutions for patients and physicians.

Now, I want to hand the call over to Alex to cover recent clinical updates. Alex?

Alexey Aleshin

Great. Thanks, Solomon.

Turning now to key indications. In colorectal cancer, there are multiple events worth noting. We reported the first data from our BESPOKE-CRC registry study, which enrolled patients across more than 100 centers in the United States. The study's initial results were presented at ASCO GI this year and showed exceptional asset performance consistent with prior readouts. Additionally, for the first time, it was shown that Signatera testing markedly reduced patient anxiety and over 73% of respondents. Additionally, 96% of participants reported that they wanted to continue using Signatera going forward.

The next study I wanted to highlight is the INTERCEPT trial that was done by MD Anderson Cancer Center with over 1,100 patients tested using commercial Signatera. The observational component of this study was able to characterize the impact of Signatera testing on a routine clinical practice and showed a median DFS of approximately 5.6 months between Signatera positivity and clinical relapse.

Interestingly, the investigators also presented preliminary results from the Phase II TAS-102 substudy, which enrolled 13 patients to receive TAS-102 based on a positive Signatera result. Despite the small sample size, the study is notable since TAS-102 is the same drug being used in the randomized perspective ALTAIR study.

The exciting finding was that 54% of patients had CK clearance at 3 months, suggesting high single agent activity of TAS-102 in this patient population. Compared to an untreated Signatera positive population, where our data suggests has spontaneous clearance freight should be around 3% to 4%. Additionally, this study reported a median disease-free survival of 9 to 4 months, which compares favorably to the 5.6 months I presented a moment ago from the broader observational cohort.

Though we know the study was not randomized. We believe this all provides a positive signal for the ALTAIR study. We expect the top line readout from the ALTAIR trial in Q3 of this year with full results being presented and perhaps concomitantly published in Q4. If the study is positive, we expect it to be practice changing in the U.S., in Japan and likely, many other countries.

Next, let us review our progress towards key catalysts in bladder cancer. Just to remind everyone, we currently have Medicare reimbursement, both in the neoadjuvant and recurrent sponsoring settings. While we do not talk about bladder cancer often with around 35,000 new patients being diagnosed every year, we believe this indication could become highly penetrated and well reimbursed pending the readout of the 2 studies highlighted on this slide.

We have previously discussed the randomized, placebo-controlled global IMvigor011 study that is being done in collaboration with Genentech. The study continues to enroll well, and if the readout is positive, it would form the basis for our first Signatera FDA submission, likely in the second half of 2025. We believe the advanced status of our work with the FDA gives us an advantage.

We also want to find that the prospective nonrandomized DFS data from the Signatera negative arm of this study will be presented in oral format at the European Association of Urology Conference later this year, and it may create an interim commercial tailwind is it shows convincing data that Signatera negative patients have good outcomes, especially if an improvement is noted beyond the great results we already saw in the IMvigor010 data set published in 2021.

We are also pleased to announce the MODERN study being done in collaboration with the NCI funded Alliance Group. The lead PI of the study is Dr. Matthew Golsky, a leading expert in this space, and the study design is a testament to his and Alliance's leadership and forward thinking. With the study incorporating both an escalation and a de-escalation cohort, similar to design of the CIRCULATE trial in colorectal cancer.

The de-escalation cohort has multiple similarities to the VEGA study and if it meets its primary end point, could have significant implications for patient management, making it possible to reduce unnecessary and expensive treatment in the MRD-negative patient population.

Moving on to the next slide. We were excited this week to announce expansion of Medicare's coverage of Signatera to include ovarian cancer as well as the neoadjuvant setting in breast cancer.

Ovarian cancer affects close to 20,000 women per year in the United States has a median age of diagnosis of 63 years and is the fifth leading cause of cancer death in women. Current tools, including imaging and biomarkers such as CA-125, are inadequate to guide adjuvant and surveillance decisions in Stage 2 to 4 disease.

Based on the tariffs perspective, multicenter study evaluating 69 patients across over 160 time points, we reported longitudinal sensitivity and specificity of 100% to detect recurrence with an average lead time of around 10 months.

In breast cancer, as a reminder, Signatera has already been reimbursed in the postoperative setting for Stage IIb and higher patients regardless of disease subtype. What's interesting is that up to 50% of all resectable Stage 2 to 4 breast cancer patients currently receive neoadjuvant therapy, which is any treatment prior to surgery, both to improve surgical outcomes and to assess the tumor sensitivity to systemic therapy.

However, as the NCCN guidelines themselves now, current tools available for assessing new adjuvant treatment response are not perfect. Signatera has been extensively validated in this setting, particularly through our collaboration with ISPY-2 consortium, which is a leading group we have now been working with for over half a decade to study how bespoke CTA dynamics in the neoadjuvant setting can further improve on existing methods.

In a study of over 280 patients and over 1,000 time points, we have shown that early Signatera clearance was highly predictive of therapy response, and persistent ctDNA detection was associated with 4 surgical response as well as a very poor distant relapse-free survival. We believe this expanded coverage can help inform care for tens of thousands of patients every single year.

These coverage determinations are a great way to start the year. Especially as biomarker legislation kicks in across multiple states. We look forward to additional indications from MolDX in 2024 based on our published clinical data.

Now, let me hand the call over to Mike to cover the financials. Mike?

Michael Brophy

Great. Thanks, Alex.

The first slide here is just a summary of our Q4 results compared to Q4 last year. Steve hit some of the highlights already. Revenues were up 43% and gross margins expanded by almost 10 full percentage points. On revenues, we estimate that we had roughly $5 million in true-up beyond what we typically get in a quarter that contributed to the $311 million in total revenues. So I would estimate the organic revenue number to be roughly $306 million.

Steve also mentioned some lab-related savings that helped gross margins in the quarter. The way the holiday landed this year with the entire last week of December bracketed by Christmas and New Year's meant that we have fewer cases coming in from customers that last week of the quarter. And so didn't experience a typical COGS-related expenditures, we would normally expect in a week.

It takes about a week for us to report out most of our tests so this resulted in slightly lower COGS expenses, but did not significantly impact revenue, which is only accrued on reported units.

Netting all of that benefit out from our Q4 gross margin of 51.4% gives you our estimate of roughly 49% repeatable gross margins, which, of course, still represents a huge sequential step-up from Q3 of '23. We were able to drive these results on operating expenses that were stable compared to 2022.

As Steve described, we've invested heavily to build the critical infrastructure needed to rapidly scale the business, and we believe we're in a position to drive significant future innovation with relatively modest increases in operating expenses from our current levels. This combination of expanding revenues and improving margins on stable expenses fits precisely with the multiyear strategy we've laid out in the past.

The net result of that is that we cut our Q4 loss per share by more than half compared to Q4 2022, and now have clear line of sight to a cash flow breakeven quarter as Steve described.

Okay. That's a good segue to the guidance on the next slide. We're excited to be initiating the revenue guide at $1.32 billion to $1.35 billion, gross margins at 50% to 53%. And with relatively stable operating expenses leading to another dramatic reduction in our cash burn.

While there are a lot of variables that will cause cash flow to fluctuate from quarter-to-quarter, we now believe we can get to a cash flow breakeven quarter by Q3, if not sooner. This cashes in a steady continuation of the strong underlying trends in volumes, ASPs and COGS we've seen over the past year but does not rely on upside drivers from potential guideline changes, any spike in volumes from further Signatera data or any meaningful benefit from the biomarker legislation in the calendar year.

And it's just a modest contribution from the recent MoIDX coverage decisions. That approach leads to a fairly cautious guide on further margin expansion. I would expect to start the year in the high 40s, consistent with our organic estimate for Q4, with the goal of getting gross margins to the top end of the range and possibly beyond that by Q4 of 2024.

We have also assumed a relatively modest volume contribution from Invitae accounts. We are picking up now, consistent with Steve's base case described earlier, but hope to be raising that forecast as we get more clarity on account retention in the coming months.

In our R&D organization, the team has a steady drumbeat of product launches, clinical trial work, and COGS initiatives slated to launch this year. Once those initiatives are complete, we anticipate having bandwidth to keep driving innovation in future years without large increases in spending.

The SG&A guide includes the pickup of the Invitae sales reps and several other product launch initiatives we have slated for this year. So at the midpoint of the guide, we are forecasting revenue growth well above 20%, about 650 basis points expansion in the gross margin against annual 2023 full year actual margins and operating expense growth of about 4%.

Those of you that have followed us for a few years know that we prefer to start the year with a guide that feels challenging but achievable to us. And I think there are several sources of upside that could allow us to outperform once again this year. And that's another good segue to the next slide, which just summarizes those catalysts.

We are making great progress on ASP's volume growth in COGS in our core business, as I just described. And I'm looking forward to sharing our progress on earnings calls this year as we continue to just execute on the initiatives within our control. If we can do that, I think we are in a position to outperform once again in 2024.

Beyond that, we have some potentially significant catalysts on TAP. Of course, we have the potential guideline expansion in carrier screening in 22q that Steve described earlier in the call. The timing of those updates are always uncertain and subject to change. But tentatively, you could see some society guideline updates as early as this spring.

In oncology, we are working to expand MolDx coverage to several additional tumor types and the advent of biomarker legislation in a number of heavily populated states creates an opportunity to drive commercial coverage higher for Signatera in those states.

We are excited about the ALTAIR CRC escalation in treatment on molecular relapse study readout in colorectal cancer that Solomon touched on in his remarks, which we expect to get in the summer or early fall as he described. And finally, we are really excited about a number of significant product launches in women's health and oncology we have planned for this year. Consistent with our typical practice, we will dive into each of those product launches in the first earnings call post the launch. So in summary, I don't think we've ever been in a stronger position to start the year, and we are very pleased to be sharing these updates with you.

So let me now hand the call over to the operator for questions. Operator?

Question-and-Answer Session

Operator

(Operator Instructions) Your first question comes from the line of Subbu Nambi with Guggenheim.

Subbu Nambi

You guided to $1.32 billion to $1.35 billion in 2024 revenue. This is well above Street expectations. That said, as you noted on your last slide, there are still a lot of sources of upside. To unpack this a little bit, can you talk more about the key assumptions for things that are not in the guidance specifically, how are you thinking about the potential for videos, potential ASP increases for Signatera biomarker bill 22q, potentially Renasight.

What I'm trying to get at is essentially the magnitude of upside for each of these in 2024? I can easily see our path to $50 million to $75 million in upside to your guide. When I look at these components, does that seem reasonable?

Steve Chapman

Yes. This is Steve. So maybe I'll just make a couple of comments on these different things, and then Mike, you can sort of talk about the magnitude. I mean certainly, there's a lot of opportunities for upside. You've listed a couple of them.

I think within Invitae, we're working hard to move as many of those accounts over as we can. And we think that is going well, as we said in the prepared remarks. We'll have a little more visibility as time goes on. From a guideline standpoint, all we can really do on guidelines is produce the peer-reviewed evidence.

And we feel incredibly good about the evidence that's been produced particularly on 22q and on broad panel carrier screening. Now I think it's really up to the societies and the physicians to decide what they want to do. But certainly, that would provide a lot of upside as we're the market leader in noninvasive prenatal testing.

We have a high attachment rate of microdeletion testing. And as we sit here, we believe we're the market leader as well in next-gen sequencing-based broad panel test. When you look at Signatera and ASP, certainly, there's a lot of opportunities for upside, the same with biomarker bills. So Mike, do you want to comment further?

Michael Brophy

I mean I think those are the -- really the kind of the key drivers as you kind of think about kind of catalysts and beyond. I mean I would just reiterate what we said in the prepared remarks, which are -- the underlying trends in the core business that we've been seeing the last couple of quarters have been quite strong. And if we can just continue to see those continue to hit our marks as best as we can think in a good position for '24.

Operator

Our next question comes from the line of Puneet Souda with Leerink Partners.

Puneet Souda

First of all, congrats on the quarter beyond the preannounced numbers and really great momentum you're seeing in the business. Maybe just wanted to follow up on the guide. Steve or Mike, maybe, can you elaborate a bit more just putting together the pieces here, I mean if I look at where you have guided to versus the consensus and our expectations.

I mean, you're obviously increasing the ASP on the MRD side, you have recent indication expansion that you're seeing here. Obviously, there's momentum on Panorama, ASP on Panorama from last year, carrier screening. I mean, there's a list is fairly long. So -- and then we have Invitae's volumes adding on top of it.

So maybe just walk me through sort of why this prudent guide still just given sort of the momentum you have? And also maybe if you can talk a little bit about the 22q microdeletion

timing? I know you mentioned that briefly, but what else needs to happen there? And I have a follow-up.

Steve Chapman

Yes, Mike, do you want to take that?

Michael Brophy

Yes, sure. Yes. I mean, I think like -- so to me, I think that's good. That's a good summary of a lot of the drivers we have going forward on '24, as Steve covered on the prior question. And I would just go back to -- in each of these drivers, you're going to take like some judgment around setting the guide for the year.

We want to set something that -- so clearly, as you referenced, requires really good execution. It's going to require good volume execution. It's going to require continued momentum in ASPs and COGS. We think we can deliver that. And it's just a matter of kind of setting the level of what's challenging but achievable for the beginning of the year guide. So really no change in philosophy from what you've seen from us in prior years.

On the 22q front, I think really it's the same commentary that we provided previously. The SMART trial, as we covered in our prepared remarks, we really feel like is the landmark trial in the space. Those results were excellent. They've now had time to kind of get those data out and get it published. They've been presented at multiple conferences. I think you have got or publications have now come out of that study.

And so we think that merits further guideline consideration. Of course, the guideline committees run their own show and we don't have perfect visibility into the timing of those things. And hence, you never include benefit from guideline inclusions in a guide to start the year, but we remain very optimistic about our prospects.

Puneet Souda

Got it. And then -- if I could cover on the MRD side. You had ovarian cancer and as well as new adjuvant breast cancer expansion. When do you think that starts to come in into the volumes -- just wanted to confirm they should also benefit from the ADLT rate that you have currently? And also maybe Alex can talk about it within the framework of the clinical trials that you have with ALTAIR and the new trial that you announced today, can you maybe just sort of stack them because there's -- this does look like a series of sort of data sets that enhance your position in the marketplace. But also maybe just how does all of this play into the NCCN guideline update when we do hear that? And if you have any updates on that front, that would be great as well.

Steve Chapman

Yes. So first, I'll just say on ovarian and neoadjuvant breast, we're really excited about those indications. We've got some great data and more data coming out. I think generally, once we get coverage in place, that's really when the medical liaison team and commercial team can start going out and educating physicians really about the benefit.

So that will take a little bit of time to come in. But certainly, there's volume there today that will benefit from Alex, do you want to talk about ALTAIR and the potential there for upside opportunity and guidelines?

Alexey Aleshin

Yes. Absolutely, Steve. Puneet, thanks for the question. I think as we presented in our prepared remarks, we're expecting a readout top line readout kind of in Q3 for the ALTAIR study. And we

do believe that this study, if positive, maybe 1 of the largest events in how early-stage cancer is managed in quite a while.

Just to put this in perspective, the last study that truly changed how early-stage colon cancer is managed was the MOSAIC study published in 2004. So I think there's a lot of pent-up interest in approving new treatment modalities for these patients. We believe that any positive statistically significant result will be significantly impactful for how patients are treated.

And we're frequently asked like what are some of the numbers that would be even more significant. And I would kind of guide folks to look at the MOSAIC study, which showed hazard ratio of 0.77, and an absolute risk reduction of 5%. So we strongly feel that if we want or both of these metrics, the study would be even more significant.

And then in terms of the IMvigor011 study, we're expecting top line readout for that in Q1 of 2025. And again, if that study is positive, we also believe that would significantly not just change the guidelines, but really fundamentally alter how early stage bladder cancer is managed.

So I think these are the 2 most kind of immediate binary events to look forward to. And we have many other studies currently ongoing that we'll be reading out the next year or 2.

Operator

Next question comes from the line of David Westenberg with Piper Sander.

David Westenberg

On extremely strong quarter. So I'm going to dig in to get to the guidance. I'm really happy with the guidance, but I do want to tell you the upside -- looking to the upside as well. So just in terms of the Invitae acquisition, I mean, I would assume your ASPs are higher than there is in a lot of the reproductive health areas.

And you're calling for 25% or $25 million and I think $100 million business. So can you talk -- I mean, that would imply a little bit even less than maybe, say, 25%. So can you just make -- walk me through your 50% share kind of why you would anticipate just maybe that low of picking up of that share.

And if it's share you don't really want I would assume other companies in the space would also not want it, and we maybe see a melt-up in pricing melt up in pricing in kind of those kind of accounts contemplated in the guide?

And then finally, on that one, a lot of those OB sales force sell BRCA too. I know BRCA's not that big of a business for you, but is BRCA cross-selling also something to contemplate in that. So that was 1 question. One follow-up. It will be shorter.

Steve Chapman

Yes. No, no, that makes sense, and that's a good question. So we said we're thinking somewhere in the sort of $20 million to $30 million range is a conservative number. But we also said that we think that can get up to $50 million to $60 million. So we really have to see how things come in as we look into this sort of post-acquisition window. A couple of things to note that I think are important.

I think the first thing is that the volume that we started with at the end of January after the acquisition was, I think, a decent amount less than maybe where Invitae was in the last time they reported out their volume in Q3. And that makes sense because they had announced some initiatives to reduce some of their low-margin business. So for example, some of their low cash pay business. So I think the starting point for us is different maybe than what you're what your expectations were.

Now with that said, we're working hard now to transition over as many of the accounts, which is generally the high-margin accounts because those were the ones that were remaining over to Natera. And we think we're doing really well.
Generally, when you look at these things, you go back and you look at December 4, I know this is a little bit different than that situation. But Natera has generally done very, very well in these settings, retaining the vast majority of the business. Certainly, 50% plus of the business. And I think that's what we'll see here.
And I guess last question -- sorry, I'm back, I forgot the answer. Do you think there's an opportunity there through the OB channel, and we think there's some opportunities there as well on the oncology side. So certainly, with the disruption happening, there will be some upside opportunity there.

David Westenberg

I forgot I asked that part. So just in terms of expectation, you have neoadjuvant breast, adjuvant breast, bladder, CRC, IO. Can you talk about your expectation for long? And just given that you have all these tissue types, and I'm asking you to predict a bureaucratic agency, but have you had any conversations with MolDX or expectations on MolDX and just say, you know what, this science works in every tumor type. So when does that get coverage?

Steve Chapman

Yes, that's a good question. So I think this question of pan cancer is something that I think a lot of people have asked over time. And certainly, as you start to look at the long tail of cancers getting covered, I think at some point in the future, there may be an opportunity for just kind of across-the-board pan cancer coverage.
But we haven't set up to be dependent on that. What we're doing is we're doing very thoughtful detailed clinical validations on all the different tumor types, and we're generating the data that's needed to obtain coverage. And we think that's, I think, 1 of the reasons why we're in a leadership position today is because we've done that hard work.
We generated these studies. We spent now 5 or 6 years working on some of these trials and other companies, they may come in and not put that work in and then they end up not getting coverage. So we think we're a great opportunity.
Obviously, there's more tumor types that are in submission. We're excited about ovarian in neoadjuvant breast, but you mentioned lung, you mentioned -- or I guess you didn't mention gastroesophageal, we think, is a big opportunity for us that fits nicely with the colorectal indication. So lots of upside. We're continuing to focus here and generate data.

Operator

Next question comes from the line of Tejas Savant with Morgan Stanley.

Tejas Savant

Steve, Mike, I'll spare you the question why you've decided to be prudent with the guide and take a highly different tack here. What I want to know is what would carrier screening and ACOG guideline inclusion for 22q mean in terms of gross margin upside? I know it's not baked in, but were those 2 guidelines to fall in place in the spring? What does that look like?
And Steve, on the exit of some of these lower margin Invitae accounts over the course of the year, is that something that we should be thinking about in terms of just the phasing of the gross margins through '24?

Steve Chapman

Yes, it's a good question. So let me just comment on Invitae first. And so what I mentioned there is that Invitae themselves had actually taken steps, I believe, in Q3 time frame of last year to exit some of their lower margin accounts or maybe move away from some of that business. And so that's why the starting point of where we took over in January was maybe a little bit different than what you might have seen from Invitae in Q3.

From the Natera side, when we bring this business on, it's obviously through the Natera contracts and insurance contracts and with the Natera products. And so we think the margin should be in line with what is currently now kind of an accelerating and expanding Natera gross margin. Hopefully, that makes sense.

From the upside opportunity, obviously, there's an enormous amount of upside in the guidance. We didn't include anything for 22q coverage. We didn't include anything from broad panel carrier screening. So obviously, there's upside as these things come in.

If you just think about the clinical impact and the data that we generated, we really think that, that's the most important piece. 22q is a very severe disorder. It's a leading cause of congenital heart defects causes' hypocalcemia, which can lead to seizures and brain damage at birth, if it's not treated. So this is a very serious disorder. We test for it with, I think, a very well-validated test that was prospectively done over a 7-year period. We think we've checked all the boxes for society guidelines.

If you look at the very high attachment rate that we have, I think 75% plus of our in IPT, get 22q. Obviously, there's upside opportunity, but we think it's really important that patients get access to this test and then it's covered by their insurance company.

The same thing for expanded panel carrier screening, as we said today, we believe we're the market leader in next-gen sequencing-based expanded panel testing. But there's still opportunity there as guidelines come in place both to extend the volume today. There are still customers and OB offices around the country that are ordering smaller panels.

As the guidelines come in, we think that they will transition to broader panels, which will put Natera in a good position. And there's also a lot of business today that we're just not reimbursed on where the payers maybe have a negative coverage policy where there's an opportunity to get paid and get coverage for testing that the physicians want and that we think are important for patients.

Tejas Savant

And then switching gears to oncology, Steve. Just curious as to what's your thought process in terms of time lines to reimbursement in the breast recurrence monitoring indication? I mean that's clearly the big price.

Second, can you comment on the FoundationOne tracker I mean given the broader launch in Medicare coverage here? Where you expect in terms of perhaps an attach rate by year-end '24? And then finally, the data on early detection, I believe the first readout there is relatively imminent. But just curious as to how you're sort of perhaps you've updated your thought process there in terms of the go/no-go decision in terms of the performance specs you'd like to see from that data that would be helpful.

Steve Chapman

Yes. So maybe I'll comment quickly on early cancer detection and then hand it over to Solomon to talk about breast cancer recurrence monitoring and some of the exciting data potentially coming around treatment on molecular recurrence.

So on early cancer detection, we are planning probably in Q2 to read out a case-control study that's going to include both colorectal and advanced adenoma patients. And we're excited about that readout. The vast majority of those samples were prospectively collected and matched with colonoscopy. Not all of them, but the vast majority were.

So then after that, depending -- we're going to take a look at how that data looks. Obviously, we're excited about it. After that, in October time frame, maybe sometime September, October, we're going to be reading out roughly a 1,000-patient prospective study that will be 100% colonoscopy match. That's already recruiting patients today. And then depending on the readout of there, we'll make a decision about what we do going forward as far as the FDA enabling trial.

But the way that we've set this up is that the 1,000-patient study that's going to read out in Q3, that's actually the exact same protocol that would be used for the FDA enabling trial. So if we do want to go ahead with the FDA, we just continue enrolling into that study. So it's not like there's going to be a delay about the trial.

Now as we said before, the decision for us is going to depend on what the performance of the test looks like. And everything that we're doing this year is included in our budget. It's not any additional cost. We said we're moving rapidly to cash flow breakeven. We're going to hit that in Q3 or sooner. So all of the expenses on early cancer detection will be included in that. We'll still be getting the cash flow breakeven the same schedule.

If we do decide to move forward and view an FDA-enabling trial, that would be based on us seeing market-leading performance. And that needs to be, I think, better than anything else out there from a blood standpoint for both colorectal and advanced adenoma. So Solomon, do you want to talk about breast cancer?

Solomon Moshkevich

Sure. I think the question was specifically about coverage in breast cancer recurrence monitoring. And we do have that already. Signatera was covered for recurrence monitoring in all subtypes of breast cancer, that decision came out early last year. That's been a very high demand area for Signatera.

So as a reminder, almost 300,000 new breast cancer diagnoses per year in the U.S. We estimate over 100,000 of those are eligible under the Medicare coverage, which is Stage 2b and above, and that's for both adjuvant decision-making and recurrence monitoring.

And then for many of those patients, especially in the hormone receptor positive disease, recurrence monitoring is something people do not just for a few years after surgery, but 5 to 10 Years after surgery. So that's a very important area for us to be helping our patients and we've been doing that.

Operator

Our next question comes from the line of Doug Schenkel with Wolfe Research.

Doug Schenkel

First, let me just start with the, I guess, a clarification on ALTAIR. In terms of defining success in getting NCCN guideline inclusion and driving broader commercial reimbursement. If you get 5 to 9 months of disease-free survival, is that enough? Is that a win? I picked this range because I think that's the range of DFS demonstrated in the 2 INTERCEPT sub-studies. So as we think about the readout the summer, is that kind of the goalpost that we should be setting?

Steve Chapman

Alex, why don't you take that?

Alexey Aleshin

Yes, absolutely. So I would think instead of the hazard ratio for DSS. And if the MOSAIC study is any comparator, the hazard ratio there was 0.77. And then the second thing that's usually pretty important is the absolute risk reduction. So what percentage of patients do you prevent from recurring with a new therapy?

And for that study, I think the event rate went down from 26.1% to something like 21.1% with addition of oxaliplatin. So I would use those 2 as benchmarks. I think the median DSS improvement in absolute terms, that may be a little bit difficult, and I would not extrapolate those numbers from INTERCEPT to ALTAIR. Instead, I would focus on the hazard ratio as well as the absolute risk reduction.

Doug Schenkel

The next topic I wanted to touch on is MRD competition. So you guys have had a tremendous amount of success awarding competition, defending your intellectual property estate.

There's been a ton of focus out there on how this landscape is going to evolve even with wins by Natera. There's a potential bevy of companies intending to launch new products over the next couple of years.

So 2 questions. One, can you talk about what you expect in terms of stickiness associated with existing accounts and really a material first mover advantage that you have? And what can be gleaned from your experience in NIPT, which is a -- it's a competitive market where you have what I think is a very fair to say, sticky.

I mean how much money would you need to invest to catch up with Natera, a company that's still doing more studies including one that you announced for the first time today.

Steve Chapman

Yes, that's a great question. I'll make a couple of comments and then maybe, Solomon, you can talk a little bit more about all the things that we've done as we look toward the future.

First, I'll say there is competition. We think the tumor-informed MRD companies are the real competitors here. And particularly, I think NeoGenomics is a strong competitor. Of course, they've been in joint right now, but they have a very strong footprint.

And although I think when you look at the performance of the NeoGenomics product, from an analytical standpoint, they've made some very significant claims. But if you dig into the details, they've really increased the amount of plasma input to make it seem like the test analytically performs potentially better than it does. And I think that hurts us when you look at comparative claims that they're making based on different levels of plasma input.

Now when you look at the clinical validation, what we see on the radar product, is that the performance doesn't really hold up. And we see this where analytical validation or maybe looks good, but then you look at the clinical validation and it doesn't quite look as good. So you just have to be careful of that with any competitors that are making claims about the performance of their tests.

Solomon, do you want to talk about some of the stuff that we've done? I think the investments that we've made into clinical data and clinical trials?

Solomon Moshkevich

Sure. I spoke about this in the prepared remarks as well. I would say that 1 of the most fundamental pieces here is that once a Signatera patient always a Signatera patient. So once

you've got a personalized assay designed for a particular patient, it's extremely unlikely that they would go design a new personalized assay with some other lab. And there's ripple effects to that, right?
So that means a physician's office that's testing a bunch of Signatera patients quarterly or every 6 months, that creates its own level of switching costs for that practice to bring on another lab. Now that being said, that we are not resting on our heels from that perspective. It's always been a part of Natera's core recipe to be on the cutting edge with test performance and to continue pushing the boundaries with clinical validity and utility. And I think that's where you see us continuing to invest following that strategy.
So as I -- as we pointed out on the call, we're planning to put out multiple new features and enhancements in MRD-related products over the next 12 to 24 months. And we've got a ton of investment in clinical trials. So I don't think I can give you a specific number that you asked for, how many hundreds of millions of dollars would you need to be able to catch up. But it's definitely in the hundreds of millions of dollars.

Steve Chapman

And Doug, maybe I'll just add to that a little bit. I mean if you look at the different areas Solomon broke out, you look at data, I mean we now have a significant number of peer-reviewed studies that have been published. But not only that, we have multiple randomized trials that are ongoing that have been underway, some now for kind of 5 years or something in that time frame.
And I think the key thing is with these randomized trials that the data really is only applicable to the test that was used in the trial. So I think we're seeing some groups now are coming, doing clinical validations where they're looking just at the performance of their test.
And as you go forward, that's really not going to be good enough. You have to have a randomized study that shows how patient outcomes were impacted based on using your test in the randomized study. And that's where we're going to be and that's where we think things are going as we move forward and moving away from analytical validations and from clinical validation.

Operator

Next question comes from the line of Matt Sykes with Goldman Sachs.

Matt Sykes

Congrats on the quarter and the year last year. Maybe just given the importance of the gross profit line, could you maybe just talk about your expectations for ASP trends for women's health kind of ex-potential guideline inclusion? Like what do you kind of envision in terms of ASPs for this year? And then I have 1 quick follow-up.

Steve Chapman

Mike, do you want to take that?

Michael Brophy

Yes, sure. Yes, Matt. Yes. I mean I think we expect to see stable trends in the in the women's health ASPs that we saw toward the end of last year. So as folks have followed for some time will recall when we saw really strong kind of sequential movements upward in the ASP particularly for carrier screening, but also for the NIPT product through the course of the year, and that was a big driver, along with obviously, Natera ASPs of the margin expansion you saw in the calendar year '23 results.

And now, in '24, what the guidance was is that you get the full year benefit of the ASPs that we saw in Q4. So that -- obviously, that does leave room for there to be continued improvement, and we're working every day to continue to -- 2, we can't operate to make sure that we get the reimbursement for the covered services that we think we deserve. So there's room for that to continue to improve above the expectations we've set this year. I think that's a good kind of starting point for the guidance.

Matt Sykes

Got it. And then just on Mike, again, just on COGS reduction, and you guys have done a good job. It's obviously been a key gross margin driver. As you kind of look across your businesses, where do you see the most upside for reduction in COGS whether it's in women's health, Signatera, organ health, et cetera?

Like where do you think the biggest levers are for COGS reduction this year that could actually drive those gross margins to the top end of the guide like you talked about?

Michael Brophy

Yes. I mean I think the first -- yes, the first project that comes to mind there, obviously, is the in-house project for Signatera exome in Austin. So as a reminder, we launched our exome capability in San Carlos last year, we've driven a significant portion of the volumes to the in-house exome.

And then launching in Austin unlocks another wave of cost efficiencies just because you've got more space, you can deploy more automation, so on and so forth in that Austin lab. So we're very excited about that. We'd like to have that launched in the summer or early fall.

In addition to that, though, I mean, I think we've got across each of the major products, I mean, Panorama, carrier screening and Signatera, we've got workflow launches and improvements coming this year that can drive COGS lower across the business.

And those COGS projects because, Matt, like as you mentioned, like we have a long track record of putting those COGS projects on the board, scheduling them, investing in them and then hitting our marks in terms of actually yielding the savings. Those COGS projects are in the guide. So there's not a lot of hedge in the guide for those. But again, we're excited to deploy those, and we think they can help us mature.

Operator

Ladies and gentlemen, this concludes today's conference call. You may now disconnect.