PUBLIC

UNITED STATES OF AMERICA
BEFORE THE FEDERAL TRADE COMMISSION

COMMISSIONERS: **Lina M. Khan, Chair**
Rebecca Kelly Slaughter
Christine S. Wilson
Alvaro M. Bedoya

In the Matter of **Illumina, Inc.** **a corporation,** **and** **GRAIL, Inc.,** **a corporation.**	**DOCKET NO. 9401**

RESPONDENTS' MOTION TO REOPEN THE RECORD TO ADMIT ADDITIONAL EXHIBITS AND REQUEST FOR OFFICIAL NOTICE

Pursuant to 16 C.F.R. §§ 3.43(b), 3.43(f), 3.51(e)(1) and 3.54(a), Respondents Illumina, Inc. ("Illumina") and GRAIL, LLC ("GRAIL"), respectfully request that the Commission reopen the proceeding to admit RX4067 and RX4068 (the "Additional Exhibits") into evidence, or alternatively, to take official notice of facts found therein.

As Respondents have shown throughout this litigation, Complaint Counsel's theory of harm is entirely speculative, as it is premised on the unsupported notion that Grail's purported rivals would soon launch MCED tests that would compete with Grail's Galleri test, which launched nearly two years ago, in April 2021. (*See* Answer at 2, 10; Resps.' Pre-Trial Br. at 48; Resps.' Post-Trial Br. at 20.) After a five-week trial, the ALJ agreed with Respondents, finding that the putative MCED developers cited by Complaint Counsel were at least five to seven years away from launching any kind of MCED test (ID 144-45), and that Complaint Counsel failed to show that Illumina has an incentive to harm Grail's rivals, "which undermines

any conclusion that resulting harm to competition is 'probable and imminent'". (ID 173) (citations omitted).

Nevertheless, Complaint Counsel has insisted to the Commission that Grail and its putative rivals are engaged in pre-commercial competition (CCAB 14), and that "Grail's rivals are close to commercialization and nipping at its heels" (CCAB 25). Now, two of these alleged rivals—primary complainants against this transaction and key witnesses in Complaint Counsel's case—confirmed publicly what Respondents have said all along: none of Grail's so-called "rivals" are close to launching an MCED test, and one may not even pursue an MCED test at all. *First*, at the J.P. Morgan Healthcare Conference[1], when asked about the timeline to launch Exact's putative MCED test, CEO Kevin Conroy stated:

> There's a lot unknown about what the time lines look like . . . [s]o we're talking about a number of years before this market develops. We don't believe that a lab developed test ["LDT"] without FDA approval and without reimbursement is the way that we'll probably think about making the test available.

(RX4067 (Exact Sciences Presentation) at 9.) Conroy's statement [redacted] (*see* CC Post-Trial Reply Br. at 15 (citing CCFF ¶ 1991)) and that Exact [redacted] (CCAB 14 (quoting IDF ¶ 320)).

Second, at the same conference, Natera CEO Steve Chapman provided the following update about his company's cancer screening efforts:

> [W]e have a very limited investment on early cancer detection, probably like $5 million in the range of that per year. . . . [A]lthough we're seeing great technology

[1] The conference is billed as "the largest and most informative healthcare investment symposium in the industry". *41st Annual J.P. Morgan Healthcare Conference*, https://www.jpmorgan.com/solutions/cib/insights/health-care-conference.

> improvements and we hope to be able to put out case-control data this year, the investment is very small.
> . . .
> I think when we get the results of our sort of early case control study, I think at that point, we're going to kind of have a better feeling about whether we should be pushing forward in a more significant way or not . . ..

(RX4068 (Natera, Inc. Presentation) at 11.) [redacted] (CC Post-Trial Br. at 21 (citing CCFF ¶¶ 2250, 2256.)) [redacted] (*see* RRFF ¶¶ 2250, 2256), [redacted] Further, when compared to Grail's annual R&D investments in the hundreds of millions of dollars (*see* PX0043 (Grail) at 144), Natera's $5 million annual investment demonstrates that early detection is simply not a strategic priority for Natera, [redacted] (CCFF ¶ 2217). It is unreasonable to believe that this small investment will result in an MCED test any time in the foreseeable future. (*See* RFF ¶ 451, Fig. 6 ([redacted])).

These new developments are highly relevant to the Commission's decision. The nature of the alleged "pre-commercial" competition between Grail and its putative rivals and the timing and likelihood of these putative rivals' entry on the market bear on the extent of Illumina's alleged foreclosure incentive. (ID 176-77.) In addition, these public statements undermine the credibility of Exact and Natera executives' respective testimonies under oath. The Commission should therefore reopen the proceeding to admit the Additional Exhibits.

I. LEGAL STANDARD

"[A] party may move to 'reopen the proceeding for the reception of further evidence' at any time before the Commission issues its decision." *In re Polypore Int'l, Inc.*,

2010 WL 3053866, at *1 (F.T.C. July 28, 2010). To determine whether to reopen the proceeding under Rules 3.51(e)(1) and 3.54(a), the Commission considers "(1) whether the moving party can demonstrate due diligence (that is, whether there is a bona fide explanation for the failure to introduce the evidence at trial); (2) the extent to which the proffered evidence is probative; (3) whether the proffered evidence is cumulative; and (4) whether reopening the record would prejudice the non-moving party." *Id*. at *1 (citations omitted).

Commission Rule 3.43(f) authorizes the Commission to take "official notice" of "any material fact that is not subject to reasonable dispute in that it is either generally known within the Commission's expertise, or capable of accurate and ready determination by resort to sources whose accuracy cannot reasonably be questioned". 16 C.F.R. § 3.43(f). A material fact is one "that might affect the outcome of the suit under the governing law[.]" *Anderson v. Liberty Lobby, Inc.,* 477 U.S. 242, 248 (1986). Official notice may be taken of references "generally accepted as reliable." *In re Basic Rsch., LLC,* 2006 WL 271518, at *1 (F.T.C. Jan. 23, 2006) (citations omitted). Matters of official notice include those contained in public records. *See In re S.C. State Bd. of Dentistry,* 138 F.T.C. 229, 240 (2004). Under Fed. R. Civ. P. 201, courts have taken judicial notice of public statements that "go[] to the heart of the contested issue", *N.Y. Times Co. v. U.S. Dep't of Just.*, 756 F.3d 100, 110 n.8 (2d Cir. 2014) (citations omitted), as well as "transcripts of earnings conference calls and investor forums", *SEC v. Mozilo*, No. 09-CV-3994-JFW, 2009 WL 3807124, at *7 n.2 (C.D. Cal. Nov. 3, 2009).

II. ARGUMENT

A. The Commission Should Reopen the Record.

1. Respondents Can Demonstrate Due Diligence.

Respondents can demonstrate due diligence in admitting the Additional Exhibits now. Since they were published last week, Respondents could not have introduced these exhibits any earlier. *In re Pom Wonderful LLC*, 2012 WL 3108669, at *1 (F.T.C. July 25, 2012).

2. The Additional Exhibits Are Probative of Illumina's Lack of Foreclosure Incentive and of Witness Credibility.

The Additional Exhibits are also probative. To meet its burden, Complaint Counsel must show that harm to competition is "sufficiently probable and imminent", *United States v. Marine Bancorp.*, 418 U.S. 602, 623 n.22 (1974) (citations omitted), such that Illumina has a present incentive to foreclose Grail's putative rivals. Complaint Counsel has argued (wrongly) that a present incentive exists because, *inter alia*, Grail is engaged in pre-commercial competition with its alleged rivals and because it is likely that there will be customer diversion between Galleri and putative rival tests. (CCAB 14, 20-22.) The Additional Exhibits demonstrate that pre-commercial competition is nonexistent and that the launch of these putative "rival" tests are years away, at a minimum, making customer diversion between Galleri and other tests impossible. These are "critical elements for evaluating" Complaint Counsel's claims. *See In re Polypore Int'l, Inc.*, 2009 WL 3775105, at *6 (F.T.C. Oct. 22, 2009) (evidence post-closing of the record "would directly bear on . . . critical elements for evaluating the Section 7 and monopolization charges.").

First, the Additional Exhibits refute Complaint Counsel's argument that sufficient pre-commercial competition exists between Grail and its alleged rivals. On appeal, Complaint Counsel's sole support for this argument is the pre-commercial activity of Exact, which relies

exclusively on the testimony of its CEO, Mr. Conroy. (CCAB 14; *see* IDF ¶¶ 315-20.) Yet Mr. Conroy's public statements last week [redacted] (*Supra* at 2.) This demonstrates that Mr. Conroy's testimony at the hearing is not credible, and that his testimony that Exact is competing against Grail in "prelaunch activities" and "competing for mindshare with physicians" (CCAB 14 (quoting IDF ¶¶ 316-17)) should likewise be rejected. *See United States v. Provost,* 969 F.2d 617, 620 (8th Cir. 1992) ("[W]here a witness makes subsequent statements directly contradicting earlier testimony the witness either is lying now, was lying then, or lied both times.")

Second, the Additional Exhibits provide new evidence that Grail's putative rivals are years away from launch, and may not launch a competitive test at all. As Complaint Counsel acknowledges, Illumina's alleged "incentive to foreclose or disadvantage MCED Test rivals will depend, in part, on the degree of diversion between any foreclosed rival and Grail." (ID 175 (quoting CC Post-Trial Br. at 113).) The Additional Exhibits confirm that [redacted] (CCFF ¶ 1991), [redacted] (CCFF ¶ 2256). Because no putative rival test is available on the market, current diversion is impossible. (ID 176.) The new evidence also demonstrates that both alleged Grail rivals are, at a minimum, years away from launch and much is still unknown about the features of the putative tests, or if these tests will ever even launch, providing no basis to support Complaint Counsel's argument that future diversion is likely. (ID 176.) As Mr. Conroy said, "[t]here's a lot unknown about what the time lines look like . . . [s]o we're talking about a number of years before this market develops." (RX4067 at 9.) And Mr. Chapman admitted that

Natera is awaiting the results of an initial case control study to determine *whether* to further pursue MCED development. (RX4068 at 11.)

The Additional Exhibits are also probative of the credibility of these witnesses more generally. As discussed *supra*, because Mr. Conroy's statements [redacted], Mr. Conroy's other testimony about pre-commercial competition should be discredited. *Provost*, 969 F.2d at 620.

As for Natera, Mr. Chapman's admissions vindicate Respondents' position that there is "good reason to cast doubt on Natera's claims regarding its putative MCED test and past dealings with Illumina", including because of its reputation for dishonesty. (Resps.' Post-Trial Br. at 274.) Chapman's statement that Natera has made a "limited investment" of $5 million per year in early cancer detection [redacted] (CCFF ¶ 2250 (citing (Rabinowitz (Natera) Tr. 358).) Further, Chapman's revelation that Natera is awaiting the results of a case control study to determine whether to pursue further investment into a potential MCED test confirms [redacted]. (CCFF ¶ 2256.) Natera's flagrant disregard for the truth dictates that the Commission should not credit Natera's testimony about its prior experiences as an Illumina customer in the NIPT space. As the ALJ found, Dr. Rabinowitz's concerns about the Transaction, which he claimed were born from his purported NIPT experience, "carrie[d] scant probative weight in proving that the Acquisition will create or exacerbate entry barriers . . .". (RAB at 23 (citing ID 192).)

3. The Additional Exhibits Present New Facts.

The Additional Exhibits are not cumulative, since they present new facts that did not exist at the time of trial. *See United States v. Magleby*, 241 F.3d 1306, 1316 (10th Cir. 2001) (citations omitted). Conroy's public statements [redacted] (CCFF ¶ 1991) [redacted] (IDF ¶ 320). Chapman's admissions [redacted] (CC Post-Trial Br. at 21 (citing CCFF ¶¶ 2250, 2256).)

4. The Additional Exhibits Will Not Prejudice Complaint Counsel.

Finally, the admission of the Additional Exhibits will not unfairly prejudice Complaint Counsel. Complaint Counsel took extensive discovery from third parties about the development status and launch timelines of their putative MCED tests. (*See, e.g.*, CC Post-Trial Br. at 20-21 (citing CCFF ¶¶ 1991, 2250, 2256).) This negates any possibility of prejudice. *See Otto Bock*, 2018 WL 4627651, at *3 (noting that Complaint Counsel would not be prejudiced by admission of additional exhibits when they had elicited testimony about said topic). The Additional Exhibits provide additional relevant context to [redacted]; therefore, new information demonstrating that [redacted] is relevant.

B. <u>The Commission Should Take Official Notice of the Additional Exhibits.</u>

As an alternative to admitting the Additional Exhibits under Commission Rules 3.51(e)(1) and 3.54(a), the Commission may also take official notice of the material statements contained therein: that Exact's timeline to launch its putative MCED test is "unknown" and that it does not plan to launch as an LDT (RX4067 at 9), and that Natera has invested only $5 million

annually in early cancer detection and is awaiting the results of an initial case control study to determine whether to further pursue MCED development, (RX4068 at 11).

Official notice is appropriate here because these statements are material and reliable. *First*, these are material facts which may determine the outcome of the case. *Anderson,* 477 U.S. at 248. As discussed above, these statements bear on Complaint Counsel's claims of pre-commercial competition between Grail and its alleged rivals and these putative rivals' timeline to launching rival tests. *Second*, these types of public statements are "generally accepted as reliable". *In re Basic Rsch.,* 2006 WL 271518, at *1 (citations omitted). Courts have similarly taken judicial notice of "transcripts of earnings conference calls and investor forums", *Mozilo*, 2009 WL 3807124, at *7 n.2, as well as public statements that "go[] to the heart of the contested issue", *N.Y. Times Co.*, 756 F.3d at 110 n.8.

III. CONCLUSION

Respondents respectfully request that this motion be granted.

Dated: January 19, 2023

Respectfully submitted,

/s/ Sharonmoyee Goswami

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In the Matter of **Illumina, Inc.** **a corporation,** **and** **GRAIL, Inc.,** **a corporation.**	**DOCKET NO. 9401**

[PROPOSED] ORDER GRANTING RESPONDENTS' MOTION TO REOPEN THE RECORD TO ADMIT ADDITIONAL EXHIBITS AND REQUEST FOR OFFICIAL NOTICE

Upon consideration of Respondents Illumina, Inc. and GRAIL, LLC's ("Respondents") Motion to Reopen the Record to Admit Into Evidence Additional Exhibits and Request for Official Notice, it is hereby

ORDERED, that Respondents' motion is GRANTED; and it is further

ORDERED, that RX4067 and RX4068 shall be admitted into evidence and that the Commission shall take official notice of the facts therein.

By the Commission.

April Tabor
Secretary

ISSUED:

RX4067

S&P Global
Market Intelligence

Exact Sciences Corporation
NasdaqCM:EXAS
Company Conference Presentation

Monday, January 09, 2023 7:15 PM GMT

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Call Participants

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Everett V. Cunningham
Chief Commercial Officer

Jeffrey T. Elliott
Executive VP, CFO & COO

Kevin T. Conroy
Chairman of The Board & CEO

ANALYSTS

Unknown Analyst

Presentation

Unknown Analyst

Hello. Thank you, everyone, for coming today. It's my pleasure to introduce Exact Sciences. Today, we'll be joined by Kevin Conroy, who's the Chairman and the CEO of the company, who will be providing the presentation. And then we will also be joined by Jeff Elliott, who is the CFO and COO; and Everett Cunningham, who's the CCO for Q&A. Handing it over. Thank you.

Kevin T. Conroy
Chairman of The Board & CEO

Thank you, Zach. Thanks JPMorgan for having us attend and present and to all those on the webcast and here, thanks for joining. We will be making forward-looking statements. This is our safe harbor statement. Remember these numbers, 1, 5, 7, 9, 14 and 10 million.

In 2009, I had a meeting that changed everything. I got a call from the Exact Sciences Board. They were looking for a CEO to effectively restart the company and develop a non-invasive colon cancer screening test. And the only problem is they had no R&D team left after a decade of work and no real proof of concept. So they suggested that I go meet Dr. David Ahlquist, here on the left who -- a renowned gastroenterologist, researcher scientists at the Mayo Clinic, who is focused on the early detection and prevention of colon cancer. It was a 1-day meeting. And I left that meeting knowing that I would join the Exact Sciences team, we would partner with Mayo Clinic, and we would go about developing what became Cologuard.

Well, the first thing that we did was hire Graham Lidgard, who you see here on the right, and he is a legendary molecular scientist who built the team of research and development scientists, biostatisticians, clinical affairs team, a lab team, automation team to develop Cologuard and bring it into a lab environment. It was an arduous process, highly difficult to detect colon cancer from a stool sample because you have to get that DNA out of that sample.

And for five years, so five years from that 1-day meeting, it took to get FDA approval. It took seven years to get into the main guidelines. And it took nine years from that 1-day meeting to get full commercial insurance coverage. And here we are 14 years later, and Cologuard, that test that Graham and Dave and the team develop has now started to change the standard of care. And we're proud in November that we achieved our 10 millionth Cologuard test. So 14 years to 10 million.

My friend, Dave, I promised I wouldn't do this, passed away from ALS two years ago. But he left us with this incredible mission, which was the focus on early detection and prevention to eradicate colon cancer and to expand that beyond colon cancer because as he said, look, if you're under age 85, the #1 cause of mortality is cancer. Most people in this room are under age 85. #1 thing you have to worry about is cancer. And the way -- I mean there are brilliant therapies being developed. Every year, you see more and more but the way to really impact this problem, it needs to be -- those therapies need to be coupled with earlier detection.

University of Chicago just came out with a study that said only 14% of cancers are found through screening. If you find a cancer that's not through screening, it's typically symptomatic, which means it's typically later stage, which means it has spread, which means that you're dealing with a much more complex problem.

On the strength of our Cologuard test and also our Oncotype test, our breast cancer test, we are able to invest heavily in making Dave's mission become reality. And when you look at where we are building a company around a full range of tests, this is where things get exciting.

We know that this is so critical for us to innovate in a way that we help people determine what their predisposition to cancer is, their genetic risk, new screening test to help detect cancer earlier, new tests that help diagnose and prognosticate what the outcome of that cancer is going to be like the Oncotype

test. And you have to deliver this in a frictionless environment and a technology that makes it really easy to identify a patient who is going to benefit from a test, to ordering a test electronically, to providing a surround sound, we call it our compliance engine that helps people complete a test, to a test result and the billing associated with the test.

All of that takes an immense lift and deep technological capabilities because the goal is to make sure that physicians are able to spend more time with their patients and less time with the complexities of precision medicine.

Let's talk about our screening team. The focus has been colon cancer to date. And it's a big problem. Colon cancer is the #2 cancer killer in the U.S., 150,000 new cases last year, 53,000 deaths. Unfortunately, about half of people who are in the screening age, age 45 to 85 are not up to date with screening. Please, if you're in that age group, make sure you get screened, either a colonoscopy or Cologuard, the most sensitive way to detect either cancer or precancer.

And we know that earlier detection matters. So if you're diagnosed with Stage 1 or 2 cancer, 9 out of 10 people survive five years or more. If diagnosed with Stage 4 colon cancer, 1 out of 10 people survive. That's the difference. Early detection really matters. And so the goal here is to go and get these 60 million people screened and we're doing that.

Cologuard it's a travesty that we're not getting more people screened. Cologuard is part of the solution, a big part of the solution. One of the most important features of Cologuard is it detects 94% of Stage 1 and 2 cancers. Not -- no other noninvasive test comes close. It also detects 42% of precancerous polyps, including the small ones, and it detects 70% of the largest, most advanced precancer. If you find and remove a precancerous polyp, you actually can prevent the disease. And so Cologuard being an at-home test that's easy to use, highly sensitive with 24/7 support is a test that is now really starting to take off and make a difference.

And people who are reluctant to get screened are getting screened. This is one of our customers who happens to be a physician. Here's the story.

[Presentation]

Kevin T. Conroy
Chairman of The Board & CEO

It's pretty cool. It's powerful. And we want to make sure that all people get access to Cologuard. Like Dr. Fenton, it's changing. In fact, it's life changing. And when you look at -- now the adoption of Cologuard, eight years after launch. We saw a little blip there during COVID and we have seen renewed strength. And this momentum amounts to 66% compounded growth since we launched in 2015. And we're more confident than ever that Cologuard is going to become part of the solution to go get those 60 million people screened. Cologuard is recommended to be used every three years, so there is a recurring element to Cologuard, which is a powerful one.

Now let's talk about our breast cancer and our precision oncology team. In 2019, we acquired Genomic Health and they developed an amazing test called Oncotype-DX. And what Oncotype-DX does for an early-stage breast cancer patient is it examines the tissue and it looks at certain genes and how they're expressing the RNA. And from that, they can do a calculation that answers two really important questions.

The first question is will the patient actually benefit from chemotherapy? 80% of patients early stage don't. 80% don't. Challenges, you didn't know who would benefit and who would for sure, until Oncotype came along. The second question that it answers is also an important one. What is your percent likelihood risk of recurrence? Those patients can be treated more aggressively.

These two questions, because they've been answered with randomized controlled studies, multiple studies. It is now Tier 1 recommendation. There is no peer, and nobody has invested in those studies to generate that level of confidence.

Well, here's an oncologist who really truly believes in Oncotype because at age 41, Dr. Halaharvi was diagnosed with early-stage breast cancer. And she knew that she was facing the same decision that our patients were facing, lumpectomy, mastectomy, chemotherapy, not. And she knew that she needed an Oncotype test. Her test score came back at 18. 25 or below, virtually no benefit from chemotherapy. So she could confidently make the decision to forego chemotherapy. Well, we know chemotherapy can cause other cancers. We know that it has lifelong implications. So she was able to avoid chemotherapy. And that's a powerful testament to what Oncotype has become.

When you look at what this team has done when we first acquired Genomic Health, it was a $400 million business in 2018, with 20% EBITDA margins. Today, it's a $600 million business with 40% EBITDA margins. The investment is making a difference in people's lives. And this emanates from a culture that we have developed at Exact Sciences that starts with great people and through developing incredible tests and bringing them to patients and physicians who need them, ultimately driving profitable revenue that you can invest part back into the business.

And it starts -- it truly does start with the people. We have a culture of Exact Sciences that starts with great science and great scientists. And we know that we're on this mission to deliver something that changes the lives of people. And when you look at how this culture heads through constant small -- solving complex problems one at a time over a period of 14 years, we've grown from a handful of people to 6,500 people who are focused on this mission and a special call out to our frontline team members who delivered last year coming out of the pandemic, and they -- our field team, our marketing team, our ops team, our lab team, our customer support team and the list goes on, our finance team. They delivered. It was the front line that delivered, and that's where the culture starts.

And we've been certified as a Great Place to Work four years in a row. It's something that the team takes great pride in. So everybody has ownership. And that ownership then ends up helping us develop great tests through great science. And that's what our commitment is. Don't cut any corners. Do the hard work. Not everybody does it. You do the hard work on the science, and then you are able to address big problems, colon cancer.

Our Cologuard 2.0 program. Our colon cancer blood program will have readouts this year. We're excited about that. Our multi-cancer program, the idea of one-blood draw, most cancers, and then this idea of minimum residual disease testing. If you've been diagnosed with cancer, today frequently, the answer is go home if you're not feeling well come back after your treatment. Now today, by doing a Bespoke test, you can do a blood draw and separate the world between people who are likely to recur and those not likely to recur. It's going to be game changing.

Now here's the important part. You have a great test. Many innovators forget that the next most important part is to do the hard study. In the case of Cologuard, a 10,000-patient study comparing Cologuard to the current standards of care. Nobody thought that -- people thought that was insane when we did that. It ended up in the New England Journal of Medicine. Genomic Health before us randomized studies, five different New England Journal of Medicine publications, Tier 1 evidence.

You've got to do the studies that -- if they don't turn out your way, you don't have a product. You've wasted a lot of time maybe. But you've got to do those studies regardless because that leads to commercial insurance coverage and the ability to change practice. And what you see here is an incredible field team at a national sales meeting, and they're able to convince physicians to change the way they've been practicing medicine for a long time because of the evidence that exists.

So that's part of this flywheel that keeps rolling. And this is the best, most trained, most motivated, most experienced sales team that exists in diagnostics. There isn't anything close. Everett's going to -- we'll be happy to answer questions about this incredible team.

And then this customer experience grounded in an IT infrastructure that we built is second to none based on the Epic EMR system. And the ability with all of the different tools to prompt a physician to order a test when a patient needs one. And then also makes the experience incredibly easy all the way from order to result into billing. This has taken an enormous investment but that's part of what you're seeing flow through in the operating results of the company.

So when you see this -- each one of these stars represents a health system to which through our instance of our epic EMR is integrated. That means there are hundreds or even thousands of physicians can order a Cologuard test electronically. It's powerful. It's taken us eight years to get to about 300 systems. We have another 500 to go. You can't just replicate that overnight. That is something that is unique to Exact. It means we can drop additional tests into this ecosystem and deliver an incredible experience to physicians, to patients and automate things in the future, like prior authorizations. So we're really proud of our partnership with Epic and what that is doing for patients and outcomes.

Now, we announced results yesterday, and Jeff is going to want to make sure that I read all of this accurately. So I'm not going to freelance. We're tremendously proud of what the frontline team members achieved in the fourth quarter and for the full year. It starts with growth. So you can see here that the total revenue, excluding COVID testing grew 28%. The screening team drove a 45% growth quarter -- over last year's quarter 2021. And the precision oncology team, they faced two things. Number one, we divested our prostate cancer test. And we also faced FX headwinds.

We expect that the precision oncology team to grow Oncotype from $600 million to about $1 billion. So there's plenty of room to grow there. We added $119 million in revenue year-over-year in the fourth quarter, the largest dollar amount to date and $120 million in incremental profitability. So the flow-through was over 100%, it was tremendous.

We believe that this growth and the momentum is sustainable for many years because of the strong base of leading diagnostics that we have and are bringing, so we're about $2 billion in revenue last year, a little bit more and about $1.5 billion in gross profit. For 2023, analyst consensus is [$2.267 million]. And we think that's the right way to think about this year. With the platform that we've built and the new tests that are coming, we believe that we can continue to see this momentum grow. And this big base of predictable revenue helps fuel the company.

Now one of the things that we're proud of is a year ago, we said that we will become profitable full year 2024. And not only were we profitable on an adjusted EBITDA basis in the fourth quarter, we will be profitable on an adjusted EBITDA basis for the full year 2023. The team you've seen is making steady progress, and this was a team effort. This is a result of our IT systems, our lab infrastructure, our commercial channel, all working together to make sure that we sustain growth and are very disciplined around expenses.
This preserves our balance sheet, which we expect to finish 2020 at about $630 million of cash on the balance sheet. This puts our team in a tremendous position to bring innovations to physicians and patients. And what started with 1-day meeting with Dave Ahlquist, turned into 10 million people screened. And now by 2027, so four years from now, we expect that to a total of 30 million people. We're on a trajectory, and we're doing all of the small right things to continue that trajectory to make earlier detection of cancer, a routine part of medical care. That takes more than a great test. It takes a team and it takes us this amazing surround zone. There's still a huge amount of work in front of us. But Dave used to say all the time, if we can, we must. I missed Dave. Thank you.

Question and Answer

Unknown Analyst

Thank you, Kevin, for that formal presentation. So I'm going to kick off one question, and then we're going to open up to the audience. So don't be shy. I think we have a mic running around. [Tricia] is going to be there. But Kevin, you kind of touched about this in the presentation a little bit, but can you just talk about the key drivers in Q4?

Kevin T. Conroy
Chairman of The Board & CEO

Well, there are -- let me start, and then I'll pass it to Everett and Jeff. Much of the strength in Q4 comes not from Q4, but investments that we have made over a long period of time. And the three things that come to mind is brand awareness, the quality of the test -- the performance of the test, the commercial team, this field team is really humming and then all of the small -- the prompts, the digital experience, the text, the reminders, those things led to -- are leading to growth. But let me pass it over to Everett.

Everett V. Cunningham
Chief Commercial Officer

Yes. I'll mention a couple of things. I spend a lot of time in the field with our internal team and with customers over the last couple of quarters. People are accepting Cologuard as a first-line treatment for colorectal cancer screening. It's no longer a novelty. People know about it. I would say that our surround sound has really taken hold, meaning our field is out there. We're better deployed. We have better tools. Jeff's team has equipped us not just with data nationally but data at the market level, so we know exactly which target to call on and win.

Our marketing team, the marketing campaigns that we put in place throughout the entire year is really starting to take hold and we're really focused on campaigns for the 45 to 49 cohort and you -- as Kevin said, 9 out of 10 adults over the age of 45 are seeing a marketing campaign every single day, which is phenomenal.

And then lastly, just that surrounds sound that we get help with IT making it easier to prescribe Cologuard every single day because we're electronically interfaced. The focus and help that we get from our operations team, making it easier for us to get to our targets. That's -- that momentum, that discipline in the commercial organization, we put in place at the beginning of the year, and you're just seeing it just gain momentum throughout the year.

Jeffrey T. Elliott
Executive VP, CFO & COO

What really excites me about this is the sustainability of the growth. Kevin talked about the size of these markets. There's a lot of people out there. It's 60 million right now who are unscreened. So there's years and years of growth ahead for Cologuard and then gets even more exciting. This platform we've developed gets even more exciting as we drop new products in. So we've built a power extension here that keeps getting better with the time. That flywheel Kevin showed. Sustainability of growth, that will be a hallmark of Exact for years to come.

Unknown Analyst

Does anyone have any questions or?

Kevin T. Conroy
Chairman of The Board & CEO

I can restate.

Unknown Analyst

[indiscernible]

Kevin T. Conroy
Chairman of The Board & CEO

So the question is around the multi-cancer test. What's the time line to launch? And also, what are the challenges around reimbursement.

Let's first talk about what a multi-cancer test is and what the goal is. A blood-based multi-cancer test. Interestingly, in 2009, the second part of the day with Dave Ahlquist at the Mayo Clinic was he had this crazy notion that you would do a blood draw and look at methylation markers to detect all cancers. And I thought that was insanity. I mean I was so far out there. But GRAIL and other companies really started doing good work to evaluate whether it's achievable. And in fact, it is. You can detect most cancers through a blood draw. Now not all cancers but most types of cancers and maybe ultimately half of cancers through a blood draw. And what does that do?

At a population level, if you want to take the #1 killer for people under age 85, start to screen them because 2% of them are walking around with cancer and don't know it. And if you can shift detection from Stage 3 to Stage 1, half the time or Stage 2, half the time, you all of a sudden change outcomes in a massive way and in a way that you can't do it with therapies alone.

So what are the time lines? There's a lot unknown about what the time lines look like because you have to run large prospective studies. You have to secure FDA approval and ultimately, get Congress to allow Medicare to pay for a new test, which we think is achievable. And then also you need to get into guidelines. Well, the guideline groups have never looked at anything like this.

So we're talking about a number of years before this market develops. We don't believe that a lab developed test without FDA approval and without reimbursement is the way that we'll probably think about making the test available. More like Cologuard do the years of work and the clinical work and ultimately, then payers will see, oh, if we can do stage shifting from Stage 3 where we're spending $300,000 on a patient to Stage 1 where we can do surgery with curative intent, changes everything.

So more to come, hopefully, this year, Congress passes a law giving Medicare the authority. There is over half of Congress, Democrats and Republican equal number are co-sponsors. Let's see if we can get the bill passed.

Unknown Analyst

I guess I have another question then as well. You mentioned great progress on reaching profitability ahead of schedule and everything. What do you think is driving that progress?

Kevin T. Conroy
Chairman of The Board & CEO

Well, Jeff, why don't you take this one?

Jeffrey T. Elliott
Executive VP, CFO & COO

Yes. So Kevin talked about the years of focus in building up the two big brands, the two biggest brands of all of diagnostics. And you're seeing that momentum continue. The growth we delivered in Q4 is sustainable. If you look at what's driving it, there's not just one thing. It's the sales force, it's Cologuard rescreens, as Kevin talked about, you repeat Cologuard every three years.

It's an expanded population, this younger population, now indicated for screening the ages 45 to 49 and it's all those things plus combined with the platform we have. And by platform, it's this Epic foundation that's so powerful, allows us to engage with patients and do it efficiently. It's our sales force that Everett help build out. 1,000 people out in the field educating doctors, growing the business, that going forward doesn't really change much, right?

You look at last year in '22, our sales and marketing expense was actually down versus '21. In '23 now, we expect it to be flat down again while we continue very robust top line growth. That foundation allows you to scale efficiently. Kevin talked about some numbers in Q4. Our Q4 incremental adjusted EBITDA margin was over 100%. Now we're not going to get that level every quarter. But you can see how this business was built to scale with an ultimate goal of generating sustainable top line growth, margin improvement and cash flow.

Unknown Analyst

I guess another question building off of that. You mentioned -- you dove really well into that. When you think about growth and profitability in this environment, how do you kind of weigh that trade-off and what do you think is going to be more important going forward?

Kevin T. Conroy
Chairman of The Board & CEO

We have made investments over a long period of time, and I think investors have been incredibly patient and they were asking themselves a question, "Hey, look, do you need to spend $1 in sales and marketing to create a $1 of revenue?" And it wasn't entirely intuitive because you've never seen a diagnostic like Cologuard launched into primary care. And a primary care launch is like a jumbo jet taking off. It takes a long time but once it gets airborne, there's momentum to it.

So we have already invested in a meaningful way. And looking forward, I think what you'll see is more flattish sales and marketing expense. But Everett, maybe you can touch upon how and why.

Everett V. Cunningham
Chief Commercial Officer

Yes, I look at it as a change of mix, especially when it comes from commercial. We invested in 2022 in our health systems team. We knew that we were going to get a lot of growth from our top 250 health systems. So at the beginning of the year, I took a lot of resources from part of our organization and really invested in health systems.

What we've done in health systems has been amazing. We've developed different partnerships, not just at the physician level, but we're calling now on IT to making sure that we can get electronically interface. We're calling on quality measure leaders at the health systems. They have a goal and quality measure to hit with colorectal cancer screening. And so now they're coming to us saying, how can we use Cologuard to hit that growth, not only hit the growth, but get patients to use our back end to be adherent to the test.

So that's a great example of just not just reducing costs, but changing the mix of cost to get more growth, better return and set us up for the future.

Unknown Analyst

You mentioned during the presentation that you expect the Oncotype-DX program or product to grow from $600 million to $1 billion in revenue, and you also doubled margins from 20% to 40%. Could you give a little bit more color about the plan to achieve that growth in the time line? And then what drivers were in the margin increase?

Kevin T. Conroy
Chairman of The Board & CEO

Sure. Why don't -- I'll start with the top line growth and pass it over to Jeff. Oncotype in the U.S. is used by about 70% of HR-positive, HER2-negative Stage I/II breast cancer patients. And so it's about 70% of those patients get on to -- get this class of tests and Oncotype has about 90% share.

Outside the U.S. in major markets, penetration -- class penetration is only about 25%. So there is huge growth outside of the U.S. Today, that's approaching $150 million business, that's where we see most of our growth. Japan will come online this year. There are things that we're doing in India, other major markets, Brazil to get much greater uptake. And since it's practice changing, it's life changing. We know

that we can do this so we're going to keep investing internationally. There's still some growth in the U.S., but you're starting to see peak adoption in the U.S.

Jeffrey T. Elliott
Executive VP, CFO & COO

So the exciting part about the growth going forward is that the foundation is already there. When you look at the international markets, which will drive most of the Oncotype growth going forward, we're global. We already do business in over 90 countries, either direct or through distributors, but that foundation is there. So as we scale and get broader reimbursement and launch in new countries, the margins fall through at a higher rate. So I feel good about it. Japan could be our biggest market outside the U.S. It's been a long time in the works. I'm confident that we'll launch this year.

The other exciting part about this business is the foundation that it provides for other products that we launched. Kevin talked in his remarks about MRD. All right. Well, MRD, when we launch an MRD test which we will before it's so long, that drops right into the commercial channel we already have. So over 90% of all U.S. oncologists are ordering or have ordered Oncotype-DX. Great. And we're already touching at least 50% of the breast cancer tissue in this country.

The MRD test on top, strong foundation. IT systems, best-in-class already. You get really good incremental margins as we grow both Oncotype and then as we drop in other new products.

Unknown Analyst

So you mentioned complex problems of the time you sort of touched on that just now. But I'm just wondering what is your imagine, what is your envisioned pathway towards that molded enrolling of once at a time in the future addition to platform.

Kevin T. Conroy
Chairman of The Board & CEO

So the question is around complex problems being solved one at a time, how are we looking at doing that with the platform. And the answer is -- is the question more around products or the ecosystem?

Unknown Analyst

Products [indiscernible]. What's the vision towards that.

Kevin T. Conroy
Chairman of The Board & CEO

So the vision towards that from a test perspective is, first, focus on the core, colon cancer, no matter what. I mean if we invest $100 million a year of R&D for what will come shortly a $2 billion brand, that is a no-brainer. Keep making it easier for -- get the insights from patients, like here's one insight. Women don't like the larger box to return it to UPS. And they don't like to leave it on their front stoop either. That is -- it's a headwind to getting more people screened. Okay. So we have a team of people working on a smaller collection kit.

We don't talk about that much. But these are like -- you see dozens of these improvements. We're going to keep investing in the core colon cancer, colon cancer blood program. We've talked about that a lot. We see that more as a niche for people who refuse colonoscopy or Cologuard, because the performance is just nowhere close. But that's an important program, and it can drop -- that test will drop right into this platform.

Secondly, minimum residual disease testing. 3% market adoption penetration today. Natera has done an amazing job. It's really a terrific company that has led the way here. Well, we have an advantage because, as Jeff said, half of all breast cancer patients in the U.S., their tissue comes to our lab in Redwood City. And we know which ones are at the highest likely risk of recurrence. And if you are at a high risk of recurrence as an early stage breast cancer, the next test you want to get is do you still have some circulating tumor in your blood. So we launched that.

MRD program second. Maybe you invest $50 million a year for a period of time to access a $15 billion opportunity. And then finally, MCED measured because it's a swing for the fences. It's a number of years. That's kind of the third big program. And then we have a small program around liver cancer, one around esophageal cancer and one around uterine cancer. All from the same core technology that Graham and Dave and team developed a decade ago.

So you can leverage that with our lab capability, our team capability, and it really -- that's what there has to be discipline there. It has to be the core part of our mission. We're passionate about it. The team is focused on doing it, and it's a financial driver. That's how we look at Exact Sciences.

Unknown Analyst

Sorry, we got one time for one more question. So I'm just going to leave it to you. What are people missing on Exact Sciences and how do you want to people remember this?

Kevin T. Conroy
Chairman of The Board & CEO

I think the fact that there are 60 million people out there that are not up to date and they're screening, and we're going to go get those people screened. And it's going to take time. But what you're going to see is consistent growth to what we believe eventually Cologuard will be a $7 billion test. That's what we believe. And more importantly, we think that if you look out 10 years from now, you can write this down, I think that 53,000 people comes down to 25,000 people. When you drive screening from half the population to 80% of the population, it changes everything. And that's the path we're on.

I want to say we truly appreciate the support of investors. This has been a long journey, and it's because of your support that we're able to invest. So thank you very much.

Unknown Analyst
Thank you, everyone.

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S&P Global
Market Intelligence

Natera, Inc. NasdaqGS:NTRA

Company Conference Presentation

Tuesday, January 10, 2023 5:45 PM GMT

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Call Participants

EXECUTIVES

Steven Leonard Chapman
CEO, President & Director

Unknown Executive

ANALYSTS

Ruizhi Qin
JPMorgan Chase & Co, Research Division

Presentation

Ruizhi Qin
JPMorgan Chase & Co, Research Division

All right. Good morning. I'm Julia Qin, lead analyst covering life science tools and diagnostics at JPMorgan, and it's my great pleasure to introduce you to our next company presentation by Natera. And with that, let me turn it over to Steve.

Steven Leonard Chapman
CEO, President & Director

Great. Thank you very much. So this is the standard safe harbor information. Many of you know Natera, but we are today the market leader in cell-free DNA technology. We launched our first test, Panorama, in 2013, which is a noninvasive prenatal test. We were the fourth company to market. And today, we believe we have more than 50% market share. In 2020, we expanded, use the same technology to move into the field of oncology and also into Organ Health. Looking across the portfolio, in women's health, we now have a full suite of services that we offer to physicians. Panorama noninvasive prenatal testing, Horizon screening and the Empower hereditary cancer testing. In oncology, we have our Signatera MRD test; Altera, solid tumor comprehensive genomic profiling; and as you know, we're working on early cancer detection product. In addition, the oncology sales team is now also selling the Empower hereditary cancer test to breast surgeons and oncologists. In Organ Health, we initially launched our Prospera donor-derived cell-free DNA test for kidney transplant recipients. We've now added that to heart and lung. We also have a germline test that looks at patients with chronic kidney disease that we're distributing to the general nephrology practices. And I'll talk a little bit more about each of those as we go on. Now one of the core drivers of our success is that our products are supported and driven by strong real-world peer-reviewed evidence. Today, in the women's health space, we have more than 77 peer-reviewed papers. In oncology, in support of the Signatera technology. We now have 39 peer-reviewed papers. And in Organ Health in support of our donor-derived cell-free DNA and chronic kidney disease products, we have 24 peer-reviewed papers. Cumulatively, we've studied more than 1.3 million patients.

Now when we look back at 2022, we had a great year. We processed more than 2 million tests, which is year-on-year growth of 30% and we performed greater than 190,000 oncology tests, which was growth of greater than 150% year-on-year. Now in fact, these numbers would have been better. But because of the flooding that occurred right at the end of the year, we, in fact, had to not a session samples for a day or so, and that sort of delayed things. But again, we're usually conservative with these estimates. So we came in above these numbers, but we just wanted to give you a sort of a benchmark to work from. We saw a strong oncology momentum, greater than 25% of oncologists use Signatera in the fourth quarter. We now have 39 peer-reviewed publications. We got Medicare coverage for muscle-invasive bladder cancer this year -- or in 2022. That was the fourth coverage decision for Signatera. We published a landmark SMART 22q deletion study, and we got ACMG guidelines for 22q We published 12 papers in health last year, including the heart and lung validation studies and including Trifecta, which is the largest prospective fully match study ever performed in the field of donor-derived cell-free DNA testing in kidney.

And now we're in a great position to scale and we have big potential catalysts that will provide a lot of momentum as we move forward. So looking at volume, as I mentioned, we've seen excellent growth in volume. And this is coming across all areas of the business. We're seeing record volumes in each of the business units, but the growth is now being particularly driven by oncology and the rapid uptake of Signatera. So we were really pleased to come in significantly above 190,000 units. As I mentioned, we did have that flood impacting our operations at the end of the year. We were pleased to see significantly more than 25% of oncologists using Signatera in the fourth quarter. And interestingly, we're seeing very strong support in the academic centers as well.

So in Q4, greater than 90% of the NCCN academic centers in greater than 87% of the NCI academic centers use Signatera in their practice. So we think that's pretty impressive as well as the uptick now significantly above 25% of oncologists using Signatera. Q4, again, was particularly strong. We saw the

highest number ever of new patients coming in using Signatera, the highest number ever of record of recurrent patients and the most physicians using Signatera that we've ever seen in the quarter. So again, very strong momentum. Now I want to take a step back to look at women's health. One of the great news stories at the end of the year was ACMG coverage of 22q. Now 22q is a very common condition that has a very significant clinical utility behind screening. When you compare the incidence of the disease to other diseases that ACOG recommends, it's actually exceptionally common. So short -- or just second behind trisomy 21, 22q is the most common genetic disease that's recommended by ACOT. It's more common than cystic fibrosis. It's more from the trisomy 13 and 18, and it's more common than SMA testing.

When you look at the clinical utility, this is the leading -- one of the leading causes of congenital heart defects. It's also one of the leading causes of inherited schizophrenia, patients that are born with this disease are very difficult to diagnose. In fact, the average diagnosis time is about 4.7 years. And interestingly, treatment with calcium at birth can prevent seizures and brain damage caused from hypocalcemia. So there's a very strong intervention that can take place to help improve the lives of these children. It's for those reasons in addition to the performance of the test in the SMART study that ACMG has come out and issued a positive guideline. You can see their recommendation. ACMG suggests that noninvasive prenatal script for 22q deletion be offered to all pregnant patients. So we think this is a great move in the right direction by the societies and we were very pleased with the performance of the test in the SMART study. We saw high incidence, about 1 in 1,500. We saw very high sensitivity, 83% overall clinical sensitivity, and that's for all 22q microdeletions, including those that are below 2.5 megabases. So when a lot of groups talk about the performance data, they're talking about only those microdeletions above 2.5 megabases.

Now we're including all microdeletions -- all 22q microdeletions in that 83%. When you look at those just above 2.5 megabases, our sensitivity was actually greater than 99%. Specificity was also very high, leading to a positive predicted value of greater than 50%. Now if you look at historical screening tests like the screen or first trimester screening, the biochemical screens for Down's syndrome, they generally have a positive predicted value in the range of 3% to 5%. So we're talking about orders of magnitude better than the historically accepted positive predicted values for screening tests.

We look forward to seeing what happens as the year goes on with other societies. Now I'm going to move into Organ Health. So we -- there's a significant opportunity in both the transplant setting and the chronic kidney disease setting. When you look in the transplantation and donor-derived cell for DNA, we think there's about 1.2 million tests per year as the total available opportunity. We think that's only about 10% to 15% penetrated. We have validated tests that performed very well on market today across all 3 of these indications. When you look on the right-hand side, screening in the chronic kidney disease setting, this is a very underpenetrated opportunity. And we think as time goes on, this could end up being one of the biggest opportunities out there. About 10% of the population today in the United States is diagnosed with chronic kidney disease.

There's been studies in the New England Journal of Medicine that show roughly around 10% or more of those patients actually have a genetic etiology. And it's been suggested that when a patient is diagnosed with a genetic etiology that more than 50% of the time, there's an intervention that can be taken. So these are the types of statistics that I think set up nicely for very high clinical utility and very positive use case for genetic screening. Now a couple of key happenings in Organ Health. The first is Prospera Heart has now -- or the category of testing donor-derived cell-free DNA testing has now been included in the guidelines with a Class 1 Level B recommendation. So we think this could pave the way for us to get both Medicare coverage and commercial payer coverage and see an increase in the TAM.

A couple of things to look out for in 2023 are 2 big studies that are coming out that are already completed enrollment. The first is the DTRT study. This was an NIH-funded 7-year multisite prospective trial in the field of donor-derived heart testing that has more than 2,000 plasma time points. So the results are in. They're being looked at by an independent third party right now, who's leading the publication. We expect that to be out in the first half of 2023. This will be one of the most significant papers that's ever been published in the field. Next, if you look on the right, I talked about chronic kidney disease testing, the RenaCARE study, which was a multi-site perspective study that looks like the nice utility of testing patients with chronic kidney disease using a multi-gene panel. The results for that are also in the papers being

written and is going to be submitted in Q1. We think this could be a very impactful study as well that could open up that opportunity that I shared previously.

Okay. Now moving on to oncology. So a lot of our growth is coming from colorectal cancer. And if you recall we think an estimated opportunity there of greater than 1 million tests per year. There's 2 primary indications. The first is adjuvant treatment decision-making. So is the patient MRD positive, yes or no? Should we treat that patient with adjuvant chemotherapy? And then the second is recurrence monitoring. So today, the doctors may use CT scans or but unfortunately, 85% of patients that recur are diagnosed too late for the physician to do a surgical intervention. We think with Signatera in doing longitudinal monitoring, we can identify these patients early and allow the physician to intervene and potentially save the patient's life. So we've supported the use in Signatera in colorectal cancer with multiple peer review papers. But one of the most exciting is the CIRCULATE study that was presented at ASCO in GI in early 2022, about a year ago now. Now that was the first 1,000 patients enrolled in the study with 12 months of follow-up. And what we saw was excellent prognostic data. So very high disease-free survival rates for patients that were MRD negative, disease-free survival rates in the 50s for patients that were MRD positive. So a good distribution there between the 2 cohorts of patients. Very high hazard ratio of 13.3, and then the sensitivity from a single time point taken 30 days post surgery, was 67%. So we were able to identify from 1 time point, patients that would later go on to recur. Now if you do longitudinal monitoring in multiple time points, the sensitivity gets up above 90%, but this is just from that 1 single time point after surgery.

Now what was even more exciting was not just the prognostic data, but it was the predictive data. And this was really the first time the predictive data had been shown. If you're positive, what does that mean for your care? Should you get chemotherapy or not? If you're negative, what does that mean? Will you benefit from chemotherapy. And what we were able to show is that patients that were MRD positive benefit from adjuvant chemotherapy and patients that are MRD negative, in fact, don't benefit from adjuvant chemotherapy. We also were able to show that clearance of ctDNA was predictive of treatment efficacy. Now these are big findings. And what we're really excited about is that the study has continued to advance -- and now the 18-month follow-up on these patients has been packaged and submitted for peer review, and it's now been accepted by Nature Medicine. And we think that will be published shortly, potentially as soon as this month, and that could be a key opportunity to open up the next leg of growth in colorectal cancer testing and potentially an opportunity to submit that paper to the NCCN guideline committees and to commercial payers. So we've seen the consistent results across all different tumor types now at this stage, colorectal, breast, bladder, lung, but we've continued to validate. Now you can see on the right-hand side, multiple different tumor types that we've tested Signatera in melanoma, multiple myeloma, gastrointestinal, head and neck, pancreatic, ovarian, and they're all showing the same things. If you're MRD positive, your destiny recur with a very high positive predicted value. And if you're MRD negative, your disease-free survival is going to be much better than it is if you're MRD positive.

Our peer reviewed publications continue to go along at a very high clip. We now have 39 peer review publications. And one of the things that we're most excited about, and we showed this slide, I think, on the Q3 earnings call, at that time, we said in the next 6 months, we're going to have 7 additional peer-reviewed papers that have more than 500 plasma time points. To my knowledge, no other company has published even 1 paper that has 500 plasma time points in the MRD setting. We're going to have 7 that are published at that time, we said in the next publisher accepted in the next 6 months. Now we're executing on that. We've now had gastroesophageal, which is the fifth largest cancer type in the United States, accepted and published with 940 plasma time points. We just had our anal cancer paper published with more than 800 plasma time points. We've had the circulate study with 7,000-plus time points accepted. We've had our melanoma study with greater than 500 time points accepted. And we still have 4 additional studies across colorectal, breast and pancreatic that we're waiting to have accepted.

So this level of data really has served to build I think a very strong foundation for us to go get Medicare coverage and to get support from physicians and committees. So when you look at our current coverage position, we have coverage from Medicare for what we believe represents about 2.3 million tests per year. But you can see the expanded future opportunity is up to about 13 million tests per year. So as we start to submit for gastroesophageal for breast, for lung, for some of these other indications like melanoma, we're going to start to be able to tap into that additional opportunity as we further penetrate colorectal and get

more than the current share that we have there today. We're also expanding the opportunity. We can do that without validating a new test every time we go into a new indication. It's the same test, it's the same protocol. It's validated now in the pan cancer opportunity. And we just run the same test, it doesn't matter what your tumor type is.

So I want to just take a step back in oncology and kind of summarize what we think are the key strengths, but also the key investments that we've made. We've invested an enormous amount to get to where we are today, and we've built a huge moat around the product and around the opportunity. So the first is on the commercial side. We have a very large pan cancer sales team, customer service team and medical affairs team. In fact, more than 350 people across across those departments are dedicated in oncology, and that's already built into our operating expense, calling on community oncologists and academia.
We're now accepting pan cancer testing coming in ahead of reimbursement. Now that's costly for us to do because, generally, the insurance companies aren't paying for those tests, but we think it's important to generate evidence to help move the market forward. We've done excellent in executing our market access and reimbursement strategy now with 4 different coverage decisions. We think this year, we're going to submit additional 4 tumor types to Medicare, and we're going to see the first commercial reimbursement decisions for Signatera.

We've executed a very strong user experience, and we built scale. So we have phlebotomy capabilities, physician portals we're integrated, preinstalled on all of the Epic systems when people upgrade to the new software. We put extensive investments into COGS into scaling up and building the lab. As I mentioned, we now have more than 75 customer service people that are dedicated to the field of oncology. So the type of scale investment that we made is very significant, and I think hard to replicate for somebody new coming in. Now most importantly, our data leadership, 39 peer-reviewed publications now for Signatera is unprecedented, but that's just the beginning. We have more than 100 clinical trials and data sets that we're working through that we're going to be reading out over the next couple of years, including some of the most significant trials ever to be done in the field. Now we're not stopping just where we are today. We're working on improvements to the Signatera technology, and we're also working on a portfolio of tests that are going to surround Signatera. So that when we put our big commercial team to work, they're not just selling Signatera, they're selling the additional content as well that surrounds that.

Now 2 quick things. As I know, I'm 1 minute over here. In addition to our investments that we've made in our direct team, we're also pleased to announce our partnership with Foundation Medicine. We think this is a great opportunity. As many of you know, they're building a FoundationOne tracker off of the FoundationOne CDx. So there's no need to really do the whole exome sequencing. They're just building it off the comprehensive genomic profiling that they're already running today. They have a significant base of installed patients that as soon as we move into full launch, we're in pilot launch right now in the clinical setting, we can just flip the switch and run Foundation tracker for any patient that has historically gotten FoundationOne CDx or that prospectively gets FoundationOne CDx. It's now fully available. It's no longer in pilot mode in the IUO setting. So of our prospective pharma studies. So we're looking forward to continuing this partnership. They've been a great partnership. We submitted to MolDx off the strength of 2 peer review papers that have already been published, and there's a lot more data coming.
Now finally, just want to summarize today, we have established products with strong market position. Unmet clinical needs are being met with our products. We have strong volumes, excellent ramp coming out of '22. We have a leadership position in peer-reviewed data. We built and made a major investment to the commercial team. So now we're at peak levels of spending in R&D and commercial and operating expenses. We don't have to increase that in order to meet the goals. We can keep our operating expenses flat and go out and grow the volume on top of this on our path to getting to cash flow breakeven. So in the future, we have big catalysts coming. Microdeletion guidelines, NCCN guidelines, commercial payer coverage, additional MolDX coverage opportunities. We're investing in COGS and scalability, while we keep our operating expenses flat, so we can get on a path to cash flow breakeven in the range that we described previously. So with that, I'll open it up for Q&A. Thank you.

Question and Answer

Ruizhi Qin
JPMorgan Chase & Co, Research Division

Thank you, Steve, for the great overview. Definitely a lot to look forward to in '23. So perhaps we can start with 4Q volume trends. You obviously announced very solid numbers. And very robust trends for Signatera volume as well. Maybe talk about what surprised you to the upside and give us an update on the current mix between covered and noncovered indications and any notable pieces to call out?

Steven Leonard Chapman
CEO, President & Director

Yes. I mean, look, I think to be where we are in the launch and to be seeing this level of support from both community and academic physicians in the ordering patterns, I think, is really unprecedented. As we mentioned now in Q4, significantly more than 25% of oncologists use Signatera. 90% of NCCN academic sensors use Signatera and more than 87% of NCI academic centers use Signatera. So that, I think, bodes very well for where the technology is going, both from a utilization standpoint and from a guideline standpoint in the future. Colorectal is just the beginning, though, as you saw on the slide. It's only making up slightly less than 1/10 of the overall opportunity long term. And so we think we're just getting started, and we're going to continue to see very strong momentum.

Ruizhi Qin
JPMorgan Chase & Co, Research Division

And how much of your current signature volume today is covered versus noncovered? And within kind of covered, how much is -- noncovered, how much is colorectal and...

Steven Leonard Chapman
CEO, President & Director

Yes. So today, we have coverage in colorectal from Medicare. We have coverage from muscle invasive bladder cancer, and we have coverage for immunotherapy monitoring. We're seeing utilization in other tumor types outside of those, and we're also seeing utilization from commercially insured patients. So when you look at -- if you consider those as sort of covered, I think together, those make up probably in the range of 75% of the orders or something like that in that range.

Ruizhi Qin
JPMorgan Chase & Co, Research Division

Got you. Now you recently noted the trend that Signatera volume growth in noncovered indications is kind of outpacing the growth in colorectal. Maybe help us understand some of the dynamics that's going on there because theoretically, we could think that it should be relatively easier push your CRC utilization volume because it is the beachhead indication, the most established in terms of data and reimbursement, et cetera. So like how much of that is driven by your intentional strategic choice to establish a footprint with as many accounts as possible and then you can cultivate these physicians over time versus how much of that is purely driven by end market demand?

Steven Leonard Chapman
CEO, President & Director

Yes. So I would say now at this stage right now, we're seeing consistent growth in colorectal and covered indications as well as noncovered indications. I think when we first enabled the kind of broader pan cancer offering, we saw an uptick, but that's now normalized, and we're seeing solid increases in colorectal, record quarters every quarter basically, along with now muscle invasive bladder really starting to tick up and continued success in IO. In fact, I would say we're rather than focusing on the noncovered indications, we're actually going the other way. So we're -- we've -- I think we've established ordering patterns for some of these noncovered indications, but we're putting our sales team's effort on the covered indications.

And we think that's the right -- we think that's the right path forward. As things get covered by Medicare, we're going to open those up. We're not rejecting samples, but we're not incentivizing our sales reps to go out and kind of focus on noncovered indications.

Ruizhi Qin
JPMorgan Chase & Co, Research Division

Got you. So between the sales force focus and your expanding indications, we should see the mix of coverage...

Steven Leonard Chapman
CEO, President & Director

Yes. The mix will be, I think, relatively stable. And as things open up, so -- for example, if we got breast coverage, we'll start to see that kind of increase relatively speaking, with respect to the broader book.

Ruizhi Qin
JPMorgan Chase & Co, Research Division

Got you. Can you remind us when the next NCCN guideline meeting is taking place?

Steven Leonard Chapman
CEO, President & Director

Yes. So we're waiting for the '23 schedule to come out. In fact, we still don't have the results of the 2022 meeting that took place in August. Like we said before, we think it's pretty unlikely that they've included Signatera into that guideline just based on the fact that the CIRCULATE study wasn't published at the time that they held the meeting. But we still think the CIRCULATE publication could be a big upside opportunity for us and look forward to that coming. I think it's possible that could get published this month. We're going to have to wait and see. And then we look forward to seeing the NCCN calendar as it's released for '23.

Ruizhi Qin
JPMorgan Chase & Co, Research Division

And you're pretty confident that with what you have, by now, it's -- it should happen with pretty high certainty.

Steven Leonard Chapman
CEO, President & Director

I mean, look, when you look at the paper when it comes out, it's a very strong paper. And that, combined with the DYNAMIC study, which was the randomized trial out of Australia, I think is a very strong position for MRD testing.

Ruizhi Qin
JPMorgan Chase & Co, Research Division

And is it still your expectation that when the guideline comes, it all endorse MRD testing in adjuvant therapy escalation only or will we see guideline for both escalation and deescalation? And then how much of the addressable volume falls into each category?

Steven Leonard Chapman
CEO, President & Director

So I think the when you look across our data, I think it's been very strong in adjuvant for both escalation, de-escalation and then also in the institutional monitoring, where we're looking at early detection of -- or detection of cancer recurrence. I think the -- from what we found, historically, physicians making a decision to not do something that they're used to doing is always a little bit of a higher bar versus them maybe making a decision to do something when they're otherwise uncertain. And so I do think that there's a higher bar for de-escalation. But I mean, the results that we've seen have been really solid across all

different indications. And I think we just have to kind of wait and see how things pan out. We'll go from there.

Ruizhi Qin
JPMorgan Chase & Co, Research Division

Great. I'll pause briefly to see if any questions from the audience. All right. Let's continue on with Signatera. So you recently discussed potential plans to develop IVD kits for Signatera. In the meantime, one of your peers recently decided to exit the IVD strategy. So help us think through the rationale there? Do you think the market is ready to embrace a more decentralized model? And like, are you ready to lock down the technology in terms of performance and everything despite the evolving competitive landscape?

Steven Leonard Chapman
CEO, President & Director

Yes. So I think this was an area of confusion actually. When we said IVD, we didn't necessarily mean distributed kits. And so in order to run interventional trials like the CIRCULATE U.S. study, for example, you have to have a certain regulatory threshold in order to do companion diagnostic partnerships and do some of the bigger trials, the Phase III clinical studies that we've announced in breast cancer that will open up that opportunity to treat patients on molecular recurrence. You have to have a CDx level regulatory status. And so when we said, look, we're going for IBD, that's no different than Guardant 360 being FDA approved or FoundationOne CDx being FDA approved. It's that same regulatory status that we're going with Signatera. We're not planning on doing a kitted strategy to bring Signatera around the world at this time, although that's something that we are open to in the future. But I think for right now, we're focusing on driving the CLIA lab volume in addition to this sort of IVD level regulatory volume out of our existing lab.

Ruizhi Qin
JPMorgan Chase & Co, Research Division

Got it. That's helpful clarification. So a couple of follow-ups. One is, how should we think about the time line on the IVD front? And then number 2 is, how do you balance kind of this need to get IVD to get spec into more companion and pharma clinical trials versus the flexibility to continuously iterate on your product because your competitors are also continuously evolving their panels for high sensitivities.

Steven Leonard Chapman
CEO, President & Director

So I mean do you want to talk about that a little bit? Sure.

Unknown Executive

Solomon Moshkevich, General Manager, Oncology for Natera. So the -- in terms of timing, which is your first question, that's going to be driven largely by the diagnostic road map that's laid out by our pharma partners. So we've got several trials that we've announced previously, and we're on the board. When Steve was presenting specifically the IMvigor011 trial in partnership with Genentech, that's in muscle-invasive bladder cancer and the ZEST trial in partnership with GlaxoSmithKline and triple-negative breast cancer and BRCA mutant HR-positive breast cancer. So as those trials get close to reading out and our pharma partners get close to submitting to the FDA for approval of the drugs in MRD-positive patients, we would submit alongside them. And talked to Genentech into GSK about how those trials are going. But we're very pleased and we're heavily invested in making those trials successful. If they're successful, that opens up a significant new reimbursed indication, presumably with Level 1 guidelines, recommendations for patients to get Signatera testing if they could fit into the current inclusion criteria of the trial, and full commercial and government payer coverage as well. So that's a very important approach, and we're -- we have a pipeline full of other studies of that nature in other indications. So how do we balance that against innovation? What we see is that the current Signatera product, which is supporting those trials, is actually nearing a pretty good level of maturity where we feel comfortable having run the thousands and thousands of tests that we've described. And we've learned a lot, we've made over 100 improvements to the assay, and we are ready to lock that down and take that through the FDA as a single-site PMA or

510(k) if the FDA sees it that way. At the same time, we can continue to innovate on our LDT assay and stay on the cutting edge there as well.

Ruizhi Qin
JPMorgan Chase & Co, Research Division

Got you. Just dovetailing on that, how are you thinking about -- what thinking on tumor informed versus too many. I think we can all see that so far, you guys have gotten a lot of success and traction with a tumor-informed approach. Do you see the landscape staying the same or maybe changing a bit going forward as tumor-naive approaches have broader panels and...

Steven Leonard Chapman
CEO, President & Director

Yes. I mean look, I think we're really focused on delivering to the doctor what the doctor wants and that we're going to stay focused on that. I think so far, what we've seen is tumor informed is being accepted very nicely. And we're continuing to see record growth numbers. We're excited about innovation on Signatera and innovation in the oncology portfolio overall. And if you look at the history of Natera, one of the things that's driven our success is continued innovation and continued improvements to the performance of the test and continued additional content. I think we're on like the ninth version of Panorama, something like that now, if you look back at the prenatal test. So we've got a lot of cool stuff that's coming. We generally don't talk about until it comes out. But we -- there's a lot of cool stuff coming on Signatera.

Ruizhi Qin
JPMorgan Chase & Co, Research Division

Sounds great. On cancer screening program, I know it's still early, but you guys are planning to share some early validation data this year. Is that right? So could you maybe give us a sneak peek of underlying technology, is it based on ctDNA only? Is it based on methylation or maybe and what kind of performance advantage can that potentially...

Steven Leonard Chapman
CEO, President & Director

I mean we really don't have any -- I think we've said before, like we have a very limited investment on early cancer detection, probably like $5 million in the range of that per year. I mean it's -- although we're seeing great technology improvements and we hope to be able to put out case-control data this year, the investment is very small. And we don't have any updates right now versus what we said previously. So I'm not going to kind of -- I'll just point people back to kind of what was said before. I'm excited about it. I think the early data that we're seeing is very strong, but it's a very low investment.

Ruizhi Qin
JPMorgan Chase & Co, Research Division

Got you. So I mean as you think about or as you make the decision of whether or not to continue to maintain investment at a modest level versus stepping it up and pushing full force, what kind of data or performance bar do you need to see to kind of make that trigger?

Steven Leonard Chapman
CEO, President & Director

Yes. I think when we get the results of our sort of early case control study, I think at that point, we're going to kind of have a better feeling about whether we should be pushing forward in a more significant way or not, we're going to do that in a way that I think makes sense where if we move forward and fund additional investments, it's going to be obvious to everybody that, that was the right decision. But for right now, our strategy is very low investment in the $5 million range, and we think that's the right approach.

Ruizhi Qin

JPMorgan Chase & Co, Research Division

Got you. Any questions from the audience? All right. Let's maybe move on to women's health. So great to see the ACMG guideline endorsement. What's your thinking in terms of ACOT time lines? And how quickly payers will follow suit?

Steven Leonard Chapman
CEO, President & Director

Yes. I think we just have to wait. I mean, I think the meeting is enabled. It could come before then or could come after or could not come. But I think we feel positive that ACMG has endorsed with a very strong guideline. And a lot of the ACMG guideline members in women's health are also ACOG members, OB and they're very tuned into sort of the status of things. You just have to go back and look at the fundamentals. Is it a common disease? Is there a cost-effective way to screen for it? Does it have a high sensitivity, high specificity, high positive is there a clinical intervention. When you look at all those things, the basic criteria that ACOG and ACMG have outlined, it checks all the boxes. And the reason why we did the study in the first place 8 years ago, was because we know that it takes this type of study in order to move the needle. And this will be -- if guidelines do come out, this would be a good example of us making an investment, doing the right study, taking the long-term approach and having to ultimately generate a guideline and coverage. And that's the same model that we're following with Signatera now with more than 100 different clinical trials that are underway. It builds a moat and it makes it, I think, challenging for others that don't put that level of rigor into the clinical data to come in and launch products successfully.

Ruizhi Qin
JPMorgan Chase & Co, Research Division

Great. Any updated thoughts on the net potential impact of the California program?

Steven Leonard Chapman
CEO, President & Director

Yes. We've actually done very well in California. I think we've seen probably a 50% increase in the volume, something in that range in the State of California. Now if you remember, the state program volume is at a much lower price because they're only purchasing a very small panel of tests. So we have a separate product that we sell for the state program in California that's not the Panorama product. I think most people are aware that there was an injunction that prevented the state from enforcing the program fully. And so we've been able to continue to offer Panorama. We've seen that volume kind of normalize now, where there are some customers that want the state program and they want that, we're able to service that. And there are some customers that want to order Panorama directly. And when the customer wants that, we're able to service that. So we have to see how things evolve. But I think being in a position that we're in right now, I think, is fine. And as things evolve, we'll evolve our strategy.

Ruizhi Qin
JPMorgan Chase & Co, Research Division

I mean you already enjoy 50 -- more than 50% market share in NIPT. So is it fair to assume that even without a California program, you can still enjoy significant market share while enjoying a much higher...

Steven Leonard Chapman
CEO, President & Director

Yes. I think the -- we think NIPT over the next 3 years is going to get up to close to full penetration and we're in a best position to ride that wave up as things continue to penetrate.

Ruizhi Qin
JPMorgan Chase & Co, Research Division

All right. We're out of time. So with that, thank you, everyone. Thank you to the management team.

Steven Leonard Chapman
CEO, President & Director

Thank you.

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January 19, 2023

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