

MONOGRAPH

ONLY ELLIGO ACCELERATES CLINICAL TRIALS THROUGH HEALTHCARE

Elligo Elite Learning Series Monograph — How Early Detection & Diagnostic Products Will Shape the Future of Healthcare

Only Elligo provides direct access to known patients with their trusted physicians and research practice management solutions to accelerate the development of new pharmaceutical, biotechnology, and medical device and diagnostic products.





HOW EARLY DETECTION & DIAGNOSTIC PRODUCTS WILL SHAPE THE FUTURE OF HEALTHCARE

To improve outcomes and increase quality of life, we must intersect with patients earlier in their disease progression. However, the development of newer, better detection and diagnostic methods is hindered by large gaps in utilization, payor coverage, and patient access. To optimize early detection and diagnostic research, we must observe the real-world use of these products and apply those insights in the design and implementation of clinical trials.

Faith Holmes, M.D., Medical Director, Senior Vice President of Medical Affairs, Elligo Health Research®, and Dawn Sauro, Executive Vice President, Research Strategy, Elligo Health Research, presented an Elligo Elite Learning Series roundtable with Xtalks, titled, "How Early Detection & Diagnostic Products Will Shape the Future of Healthcare." This roundtable was an exploration of the barriers between healthcare, patients, and new early detection and diagnostic methods and how improving the design of clinical trials in this therapeutic area will lead to a more patient-centered trial experience and faster adoption of life-improving and lifesaving tools.

In the roundtable's first section, Faith Holmes dove into the current state of cancer diagnostics, focusing on the three main ways cancer is diagnosed and why improving cancer detection should be a priority. Dr. Holmes then detailed the most common patient barriers to cancer screenings and the implications each barrier has for

early detection and diagnostic trial design. Next, she provided insight into patient-centric early detection and diagnostic trials through the lens of health disparities and diversity in research. In the discussion's final section, Dawn Sauro provided suggestions for optimizing diagnostic clinical trial operations.

Ryan Muse

Well, good day to everyone joining us and welcome to today's Xtalks webinar. Today's talk is entitled "How Early Detection & Diagnostic Products Will Shape the Future of Healthcare." My name is Ryan Muse, and I'll be your Xtalks host for today. Today's webinar will run for approximately 60 minutes and this presentation includes a Q&A session with our speakers. Now, the webinar is designed to be interactive, and webinars work best when you are involved. Please feel free to submit your questions and comments for our speakers throughout the presentation using the questions chat box, and we'll try to attend to your questions during the Q&A session. This chat box is located in the control panel which is on the right-hand side of your screen. And if you require any assistance along the way, please contact me at any time by sending a message using the same chat panel. At this time know that all participants are in listen-only mode. And please note that the event will be recorded and made available for streaming on Xtalks.com.

INDUSTRY EXPERTS



Faith Holmes, M.D.
Medical Director, Senior Vice President of Medical Affairs, Elligo Health Research



Dawn Sauro
Executive Vice President, Research Strategy, Elligo Health Research



At this point, I'd like to thank Elligo Health Research who developed the content for this presentation. Elligo Health Research accelerates clinical trials through healthcare with access to over 150 million known patients and their HIPAA-compliant healthcare data, their IntElligo® Research Stack technology, and PatientSelect identification and engagement model coupled with the largest known patient access network. Elligo's site solutions enable healthcare practices and research sites to participate in clinical trials by adaptive engagement of known patients and physicians. They accelerate the development of new pharmaceutical, biotechnology, and medical device and diagnostic products.

Now I would like to introduce our speakers for today's event. Dr. Faith Holmes has more than 30 years of experience in direct patient care and family practice, as well as hospice and palliative medicine, and 11 years of medical practice management. Her unique perspective plays an important part in building the company's network of research-ready physician practices and preparing them to conduct research. And Dawn Sauro has 30 plus years of drug and device development experience, including working for sites, sponsors, and CROs. She has experience across a broad spectrum of therapeutic areas. But her main area of expertise is in hematology and oncology. Having led several hematology and oncology development programs from first in human through successful registration, she brings us expertise in delivery to help sponsors drive results. And now without further ado, though, I'd like to hand the mic over to our first speaker for today. Dr. Faith Holmes, you may begin when you're ready.


Faith Holmes

Thank you so much, Ryan. I'm thrilled to be with you to speak about the subject today. As we all are probably aware, there are early detection products being developed across a number of therapeutic areas, including Alzheimer's and diabetes, with the use of biomarkers and AR/AI that incorporate patient data to create that phenotype for a patient who is either at risk

or has an existing disease and as yet an asymptomatic state. For today's discussion, we're going to concentrate on early detection in oncology. And I've certainly had patients in my practice come in and say, "Hey, Doc, can you test me for cancer?" And heretofore, we've really not had anything available to say, "Yes, here's something that I can talk to you about." But now we know that there is a pipeline in development.

Use of cfDNA in Maternal-Fetal Medicine

- D.W. Bianchi, et al. Noninvasive prenatal testing and incidental detection of occult maternal malignancies. JAMA 314 (2015)
- NIPT testing as an alternative to amniotic fluid sampling
- Detects fetal DNA in maternal blood
- Series of 125,000 maternal samples: abnormal results in otherwise asymptomatic pregnant women were found in almost 4,000 (3%)
- From these 4,000 cases, 10 cases of maternal cancer were identified
- Detected maternal shedding of abnormal cell lines from existing malignancy
- Since then, a tsunami of tests in the pipeline for multicancer early detection
 - Currently on market without payor coverage
 - In development via liquid biopsy



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I want to start out by looking together at this study that was published in 2015. Although we've known for many years that there's an underlying rationale for using blood tests to detect early cancer, the first really contemporary example was discovered, really serendipitously, and that came through the use of noninvasive prenatal testing as an alternative to amniotic fluid sampling, and looking for common fetal autosomal aneuploidies. In this particular instance, it was a study a little over 125,000 maternal samples. Out of those, about 4,000, or 3%, were abnormal. But within those 4,000, they found 10 cases of maternal cancer based on the cell free DNA that was detected in the blood test. And so this insight became the basis for the development of some of the clinical applications for cancer detection. One of the primary areas in early cancer detection as well that we're using is the primary focus of physicians in primary care because of the fact that they're the ones that are typically doing the screening.

What we want to do is look at the current state in cancer diagnosis in clinical practice. At this point, there are really three main ways in which patients are diagnosed with cancer. Either patients are presenting



Cancer Diagnosis and Detection – Current State

- Cancer detection/diagnosis
 - Presentation with signs or symptoms
 - Serendipitous finding during unrelated investigation
 - Cancer screening in asymptomatic individuals
- Current screening recommendations
 - United States Preventive Services Task Force (USPSTF)
 - Level A or B
 - Colon/rectum
 - Lung
 - Breast
 - Cervical
 - Note: Genetic testing for mutations – at risk

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.

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with signs or symptoms which, after they go through the indicated workup and evaluation, they end up with a diagnosis of cancer. There are also those serendipitous findings during some unrelated exam, sometimes what we call incidentalomas. For instance, if someone comes in, they're in a motor vehicle accident, there's some chest trauma, you get chest X-ray reviews, and lo and behold, there's an underlying malignancy so it really is something that's perchance. And then, of course, we do have screening exams in asymptomatic patients. Currently, we have what are considered Grade A and B recommendations from the United States Preventive Services Task Force for malignancies. There's colorectal, lung, breast, and cervical cancer. But interestingly, what we've seen is that there's still a huge percentage of malignancies that are diagnosed not through screening tests. For instance, there was a Medicare study that was done looking at 415,000 Medicare beneficiaries looking at these four types of cancer. And what they found on those when they looked at those cases was there was 15 through 13%, per instance of the lung and colorectal cancer cases that came through an emergency department visit. In addition, they found that 5 and 6% of the breast and prostate cancer came through emergency department visits. I want to make a note, just a checkmark here, because we'll address this a little bit later. It was a particular note that those emergency room diagnoses, there was a much higher prevalence of that being the case among minorities and people of lower income to receive their diagnosis that way. Similarly, a study in 2014 with the English National Cancer Diagnosis audit found that fully 20 to 64% of patients were diagnosed with malignancy after

presentation to their primary care on the basis of symptoms. We clearly have a need to find other means to be able to detect cancer. We can see some of the additional malignancies, there are recommendations,

USPSTF Recommendations – Cancer

- Prostate
 - Level C recommendation** - men aged 55 to 69 years, the decision to undergo periodic prostate-specific antigen (PSA)-based screening for prostate cancer should be an individual one.
 - ... consider the balance of benefits and harms on the basis of family history, race/ethnicity, comorbid medical conditions, patient values about the benefits and harms of screening and treatment-specific outcomes, and other health needs. (<https://www.uspreventiveservicestaskforce.org/>)
- Ovarian, Pancreatic, Thyroid, Testicular
 - Level D recommendation** - recommends against screening for ovarian cancer in asymptomatic women.
- Skin, Bladder, Oral
 - Level I recommendation** - current evidence is insufficient to assess the balance of benefits and harms of visual skin examination by a clinician to screen for skin cancer in adults.

Clinical Trials data informs recommendation levels by USPSTF and Subspecialty Medical Group Practice Guidelines

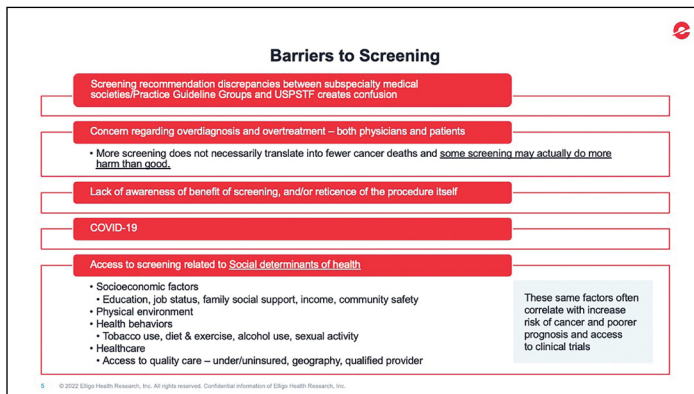
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but they fall below the A and B recommendations. They fall below the recommendations of A and B where there's either a high or moderate certainty that there is a very specific benefit from doing regular screening and asymptomatic people. These examples can bring up some of the lessons learned that we have had in previous testing for prostate cancer. For instance, initially, when PSA testing came out, we were doing PSA testing on anybody and everybody that asked. The recommendations initially were just to start testing in younger men. But one of the outcomes of that was a significant amount of false positives on the test. That led to some significant morbidity in men who were subsequently sent for biopsies and had sometimes permanent outcomes as a result of that testing. When it was in actuality, a false positive. Because of that the recommendations have been changed to men 55 to 69. And that, as a part of that recommendation, there'll be a very individual conversation with the patient about the risks/benefits balance of doing the test or not doing the test, and also taking into consideration, family history, comorbidities, their values — some people certainly have said to me, "I don't want to ever be screened because I know I wouldn't, wouldn't treat." Then, on the other hand, you may have some where, even though the general recommendation is starting at age 55, we know that in African American men there it can begin younger and be more aggressive. And so it involves a very nuanced conversation with the patient with their



healthcare provider. Level the recommendations. Give an example here for ovarian cancer and asymptomatic women. It's simply not been shown that there is value in doing broad screening, because there is a moderate or high certainty that there's really no net benefit or that the harm outweighs the potential benefits. And then there are some listed here, skin, bladder, oral, they fall under a level I recommendation. And what that means there's really just, there's insufficient evidence to assess the benefits or harm ratio to make any type of recommendation.

I think one of the important takeaways from this is the fact that clinical trial data that is collected is a part of what the USPS TF consider in coming up with these kinds of recommendations. And so it's important to include that and then, in addition, sub-specialty medical group practice guidelines will make their recommendations on the basis of at least partly considering some of these types of clinical trials. Sometimes there are some differences between what the USPS TF and a medical practice group will recommend and that sometimes is the source of confusion, which is sometimes one of the barriers to screening at this point.



Let's look at some other barriers that we see to screening. I mentioned the fact that there is some discrepancy in ovarian, and cervical cancer is a good example as well. Where the recommendations have been changed though, not everyone is following them. We've had a lot of lessons learned on cervical cancer. Interestingly, there has not been a decrease in cervical cancer deaths, it continues to be the leading cause of

death and women aged 20 to 39. And those survival rates haven't changed. A JAMA article this year talked about the fact that there's actually an increase in the number of those who are not receiving timely screening for cervical cancer.

What they found when they asked patients about it, it was a combination of lack of awareness or reticence. Some of that reticence for cervical cancer, for instance, comes from the fact that there's now we know an association between HPV and cervical cancer. And because HPV is a sexually transmitted infection, particularly in rural areas, they found that there was a reticence for women to come in for screening. Similarly, for colorectal cancer, some of that screening has now changed to include down to age 45, just because of some of the success. Some of the barriers come because of that confusion. The other thing that we have to keep in mind is concern regarding overdiagnosis and overtreatment, and that's on the basis of opinions coming from both physicians and patients. And we're going to get back to that one in the following slides. But for some people you have, it's important to realize in some malignancies, that when you screen early in a nonprogressive cancer, there is the potential to do more harm than good. And again, we'll talk about that in a little bit. Sometimes there is a lack of awareness of the benefit of screening or the reticence of the procedure itself. I've had a lot of patients say, "I don't want to get a colonoscopy." Fortunately, we have some of the other alternatives with regard to fit and peak local blood testing. But that has been indeed a barrier. In 2022, I'd be remiss if I didn't mention COVID-19. COVID-19 had a tremendous impact on the screening that people are accessing, afraid to go to the hospital when they were having symptoms as well. We saw a dramatic decrease in the diagnosis of a number of malignancies. And it truly was because people were not getting screening and not accessing care. I had someone I dealt with myself in my palliative care practice. Symptoms, was reticent to go to the hospital during 2020. And when they finally did, it was a stage four lung cancer. Those are very real barriers.



Cancer Screening Statistics – Lead Time Bias

- In the scenario shown here, a man experiencing a persistent cough and weight loss is diagnosed with lung cancer at age 67, and he dies of his cancer at age 70 (top). Five-year survival for a group of patients like this man is 0%.
- If this man is screened and his cancer detected earlier, say at 60, but he still dies at age 70 (bottom), his life has not been extended, but the measure of 5-year survival for a group of patients like this is 100%.
- Credit: O. Wegwarth, et al. Ann Intern Med, March 6, 2012:156.

<https://www.cancer.gov/about-cancer/screening-research/what-screening-statistics-mean>

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Cancer Screening Statistics – Overdiagnosis

- In this hypothetical scenario, a screening test that detects “nonprogressive” cancer — cancer that was never destined to progress or kill — results in the overdiagnosis of 2,000 people. Adding the 2,000 overdiagnosed patients to the pool of 1,000 patients with “progressive” cancers that were discovered because of symptoms artificially inflates the 5-year survival rate from 40% to 80%. The apparent dramatic increase in 5-year survival is an illusion: Exactly the same number of people died. This distortion shows overdiagnosis bias.
- Credit: O. Wegwarth, et al. Ann Intern Med, March 6, 2012:156.

<https://www.cancer.gov/about-cancer/screening-research/what-screening-statistics-mean>

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And then the other one that I think is really important to consider is what we refer to as the social determinants of health. All of these things, socioeconomic factors, whether it's educational status, job status, can they access a physician on an evening or weekend, they can't afford to miss work. There are also issues related to underinsured patients, certainly in this country. And I think what's important to realize is that this also translates to the same factors, correlate with many of them, with an increase not only risk of cancer, but also a poor prognosis, and input. The other caveat is many of these factors also play into a patient's ability or inability to be participants and have the access, the means to be able to participate in the clinical trials. And it's important for us to try to design trials in a way so that we can include patients within these kinds of categories in our clinical trials. It's important to gather data on patients. Now I want to go back in the next couple of slides, I'm not going to go through these in detail to the issue of the barriers of a lead time bias and an overdiagnosis bias. And these slides come actually from cancer.gov. And it talks about the fact that you may have someone who, without screening, is diagnosed based on symptom presentation at age 67, persistent cough, and ends up dying at age 70 of the disease. And if you just look at that, statistically, it looks like you have a five-year survival rate of 0% if you introduce an early cancer detection test, but we don't have any real means of impacting the trajectories of his disease, he may be diagnosed at age 70. But he still dies at age, is diagnosed at age 60, rather, but he dies at age 70 of the disease. But it skews the data to look like you have a longer survival rate. This slide talks

about the overdiagnosis bias. And keep in mind these scenarios that are provided really provide the extreme. It's usually not as extreme as in real life as this worst-case scenario. But many cancers are detected by screening tests that may not need to be treated. And you actually introduce additional morbidity into the patients and their families lives with that early diagnosis. And that can be psychological, it can also be financial, in that financial impact can be not only to the individual but as well to the healthcare system.

Clinical Trials Implication

- To determine if a cancer screening test reduces deaths from cancer
 - Include in randomized clinical trial
 - Screening cohort
 - Control cohort (usual care)
- Psychological/behavioral impact on subjects
 - Capture this impact on cancer screening behavior in both cohorts
- Involve physicians who will be primary group recommending the screening, having the nuanced discussions about risk/benefit
 - FM/IM/OB-GYN

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What are the implications for that in clinical trials? And let's look at that next. When you look at the things that I've just talked about, one of the things that's important is to determine if a cancer screening test is going to reduce deaths from cancer. Again, keep in mind, the goal isn't just to diagnose cancer, but it's ultimately to reduce deaths from cancers. It's important to include in randomized clinical trials of these early detection tests, you're screening cohorts who are having whatever the investigational product screening test is, but in addition, a control cohort who are receiving usual care



of the screening tests that I alluded to, as well as discussions around lifestyle modification, that can have somewhat of an impact on malignancy and having a good robust way and compassionate way of having that conversation when patients are enrolled in this study knowing ahead of time that they are, they may go into either cohort. And really needing to kind of appeal to that sort of altruism in subjects. There's also, I think, it's important to collect data on the psychological and behavioral impact. If patients are getting the multi-cancer early detection test, does that mean they just stopped getting the screening that we do know is there or will they have a different response perhaps, to symptoms that develop? Trying to capture some of that data, and as well involving physicians, who will be the primary group of folks who will be recommending screening in these early detection tests and having those kinds of nuanced discussions.

Potential Future State – Benefit of MCED

- Goal of screening is not to detect cancer, but to prevent a cancer death
 - And – detection at an earlier stage of disease to enable treatment regimen(s) which result in cure rather than a progression-free-survival existence and the associated financial toxicity and reduced quality of life, negative impact on the patient and their family/caregiving unit
- The ACE would be to have:
 - Accessibility –
 - to the testing and the indicated follow up if a positive test
 - to healthcare providers who can support discussions, interpretation, referrals
 - Cost effectiveness –
 - affordable for those who choose, and affordable additional diagnostics/treatment if positive
 - Earlier detection –
 - Sensitivity and specificity of tests to move the diagnosis further upstream in the disease trajectory

The impact of MCED testing has the potential to further increase health disparity if affordability is not addressed.

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If we look at what the potential is for a future state, for physicians in practice. The goal again, it's not to detect cancer but to prevent cancer death, and the palliative physician in me as well just wants to add, it's detecting that cancers at an earlier stage of disease that will enable us to have treatment regimens that will have more of a potential to result in a cure with less toxic modalities of treatment. Instead of later date, a disease state where you're really looking at just a progression-free survival existence, and all of the associated financial toxicity, impact on quality of life, and impact on the patient, as well as their family and caregiving unit. What would be the ace in the hole? It'd be to have that accessibility, the accessibility not only to the test,

but for the indicated follow up if they do have a positive test. In addition, involving the healthcare providers who are going to be able to support some of these nuanced discussions, interpretations, and referrals. And for it to be cost-effective, not only for those who choose the test but, as mentioned, for diagnosis and treatment. And then it not only includes the sensitivity and specificity of tests, but again, to move that diagnosis further upstream in that disease trajectory. The impact of this multi-cancer early detection, testing really has the potential, unfortunately, to increase the disparities in health, if affordability isn't addressed. And these are very real scenarios that happen. I can tell you of a 64-year-old white male who presented to my practice. He had been presented to the emergency department with symptoms and was subsequently diagnosed with widely metastatic bladder cancer. He received a neuro-oncology consult while in the hospital. And he was told to go to palliative care. And that's how he presented to my practice. Four months later, literally, the day after he turned 65, he received a call from that neuro-oncology practice, to please come in and set up an appointment to develop a plan of care because he was now a Medicare beneficiary. Those are the real, very real kind of scenarios that happen. He did get into care; it was late, and it really had more of an impact on a reduced quality of life. And he did say to me just before passing that he wished that he had not taken advantage of that. Those are the things that are really important for us to keep in mind as we move forward and the very real impact on patient care and the physicians within healthcare. We still have to move things along from the bench to the bedside.

FDA Approval/Clearance vs. Medicare Coverage Determination	
FDA Approval or Clearance	Centers for Medicare and Medicaid Services (CMS)
Based on Safety and Efficacy	Based on Population Health and Cost Effectiveness
	Sufficient evidence that a treatment or service is reasonable and necessary to diagnose or treat an illness or injury
	Applicability to Medicare beneficiary population
	National and local coverage determinations
Defined population following a defined protocol	Normal clinical conditions in a typical Medicare population



Let's look at the difference between the FDA approval or clearance of that product, and the Medicare coverage determination. What FDA looks at and bases their decisions on approval or clearance is the safety and efficacy of that investigational product. They're looking at a very defined population, looking at it within the confines of a defined protocol for a defined period of time. But what CMS looks at is that there's sufficient evidence that a treatment or service is reasonable and necessary. Those are the keywords to diagnose or treat an illness or injury, and they're basing those decisions on population health and cost-effectiveness. Looking at the applicability to the Medicare benefit beneficiary population, I'm to help inform not only national but local coverage determinations. And they're looking at it within the context of the normal clinical conditions that are in a typical medical Medicare population. With all the comorbidities and polypharmacy that's happening with this age group, there is legislation that was introduced in 2021, the Medicare Multi-Cancer Early Detection Screening Coverage Act of 2021. In that, they will create a benefit category for MCD testing because there really currently isn't a benefit category and there needs to be. The Congressional Budget Office has still not looked at it to attribute cost associated. And what they'll be looking at is the costs associated with the lives saved as compared to the benefits of early detection. Collecting data during that clinical trial phase, which will inform those cost calculations, may have an impact on the timelines for getting to when there is coverage.

Payor Considerations	Clinical Trials Implication
<ul style="list-style-type: none"> Medically necessary vs. investigational: <ul style="list-style-type: none"> Analytic validity – accurate, reliable, minimize false +/-ves Clinical validity – medically meaningful Clinical utility – test result impacts clinical decisions and improves health outcomes With multicancer testing – some benefits/harms differ by cancer type <ul style="list-style-type: none"> Benefits of test depends on cancer types/stages detected and differences in stage-specific treatment outcomes and costs 	<ul style="list-style-type: none"> Collect retrospective and prospective healthcare data on tested and non-tested (control) populations <ul style="list-style-type: none"> Cancer incidence, utilization of existing screening tools Comorbidity, medication use Collect patient and physician perspective on impact of tested vs. non-tested, false +ve/-ve impact Collaboration with Medicare Evidence Development and Coverage Advisory Committee

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One of the things that I bought in the past has always been said, “Well, whatever Medicare decides, the other third party payers will follow suit.” And we realize that's really not the case. It is less and less so. Payers are going to be looking at medical necessity versus investigational in they are looking at the analytical validity, the clinical validity, as well as the clinical utility, is it going to truly make a difference in the decision-making process in the management to prevent disease? And they very well may take into consideration the different diseases and the indolence or aggressiveness that will impact the cost of healthcare. And they may actually be considering things where you don't want to test 50 tests but put them into smaller panels or tiers. But the more information that can be gathered, both retrospectively and prospectively from healthcare data on both the tested and the non-tested control cohorts, will really help form and make those decisions. Collecting, as well, that patient and physician perspective on the impact of the false positives and negatives. And consider collaboration early on with the Medicare Evidence Development and Coverage Advisory Committee on what are some things that can be incorporated in the clinical trial protocol and designed to help them answer those kinds of questions earlier.

Other Considerations
<ul style="list-style-type: none"> Utilize physicians in community practice as investigators who will drive utilization of final product With multiple products, more likely to use one they were on as clinical investigator Ready insight to impact when subject is seen within their existing patient-centered medical home <ul style="list-style-type: none"> Psychological, financial, family influence for testing etc. Leverage data to inform additional AI/algorithms to enhance diagnostics as a whole <ul style="list-style-type: none"> i.e., Enriching New-Onset Diabetes for Pancreatic Cancer (END-PAC) <ul style="list-style-type: none"> – age, change in blood glucose and weight to predict pancreatic risk in newly diagnosed diabetics Link early symptoms/signs/lab data to a clinical phenotype along with multiomic testing Include cohorts who are under cancer recurrence surveillance <ul style="list-style-type: none"> Evaluate cost effectiveness of Standard of Care surveillance modalities vs. multiomic testing

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Next are a few general considerations which utilize physicians who are in community practice, as investigators, they're the ones who are going to drive utilization of the final product. There's going to be a lot of products out there, they're more likely to use one



that they may have been a clinical investigator on, they can also provide a really ready insight that can impact patient's decision-making process, because they're based in their patient-centered medical home. And they have a line of sight to the financial and psychological family influence for other family members being tested. In addition, leverage data to inform AI algorithms to enhance our diagnostics as a whole, that we don't think of just multi-omics testing or methylation-based platform testing as just a singular entity. But we combine that with looking at the evaluation of early signs, symptoms, lab data, which can create a clinical phenotype that may lead to early detection. An example of that is the end pack where they've developed, through AI algorithms that look at age-changing glucose changes in weight, that predict pancreatic risk and newly diagnosed diabetics. And one other consideration would be including cohorts, who are not new diagnoses but rather cancer recurrent surveillance. What's the relative cost-effectiveness between a standard of care surveillance modalities, PET scan, biomarkers, etc., versus some of these multi-omics platforms? And we're going to turn it over to Dawn now who has further insight into operational considerations in this testing.

Dawn Sauro

Thank you, Dr. Holmes. To just kind of dovetail on what Dr. Holmes has been talking about, some of the ways that we've seen across the multiple diagnostic trials that we've run at Elligo, and want to share some of the lessons learned, some best practices, and a case study. One of the most important things to consider is if there's a requirement for the EHR access and to collect


some data, it's important to focus on the data that you really need, as opposed to trying to catch too much. Because, like 12 or 18 months of complete medical records can present challenges to a lot of patients and healthcare practices where the EHR may not be the same across the different physicians that the patient is seeing over 12 months. In that case, it's not an impossible thing to overcome. But make sure that when you're setting up your trial and setting up your sites, you obtain a medical records release form prospectively so that you're not chasing the data after the fact when you're trying to close out your database.

We've discussed the control subjects earlier, and one of the things that we've found is that it's really helpful to enroll the control cohort in parallel with the cancer cohort. A lot of the times that cancer patient support systems are highly motivated to be part B control patients as they're taking their family member in for appointments. And also, depending on how your study is set up, and I'll talk about, in my case study, if you're looking for an enriched population, it leads to being able to enroll that control subject in parallel as well. These types of studies are really ideal for community-based practices that are newer to research. They're great studies for the physicians and staff to get experience with the operations of a clinical trial, but also are well suited, as Dr. Holmes just mentioned, there's the opportunity for greater ethnic diversity in these community-based practices.

And then one of the things you do need to consider and again, to dovetail on something said earlier, if the results are provided, it's very important to think about the availability of treatment to these patients and where they can be treated. And that's important with the site selection. One of the things that, I was recently at the oncology CEO roundtable meeting, and a big issue that's come up with these community-based sites that are trying to run these diagnostic trials is the site training, as well as site staffing. You know, as you're reaching out to these types of practices, you know, thinking about the volume that you're going to have, and how maybe you can manage the whole diagnostics. Or, you know, the virtual model presented another set

Operational Considerations for Diagnostic Clinical Trials

- EHR access – determine what information is required, if any
 - Obtain a medical records release (MRR)
- Control subjects
 - Cancer patients support systems highly motivated
 - Enroll in parallel
- Ideal for community-based practices newer to research
 - Ethnic diversity
 - If results are provided – availability of treatment
 - Site training
- Home diagnostics
 - Right kits to right patients, logistics
 - Participant coaching and instruction
 - Tracking – samples and inventory
 - Shipping integrity
- Site selection – Point of care considerations



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of challenges and operational, logistical considerations. There's making sure that the right kits get to the right patients and the logistics and the tracking. But then there's the training, because if the patients are doing the testing themselves at home, you know, the coaching and instruction and where are the patients going to get that training? How accessible is it? Do they understand the timing, and how is that all going to be documented? There's the tracking of the samples and the inventory that you need to take into account. But also the shipping integrity if the patient is at home and is going to be preparing the sample for shipment, how is that integrity going to be managed through the whole supply chain cycle? Then site selection really is one of the biggest things because you really need to think about that and plan. And that's really around the point of care considerations.

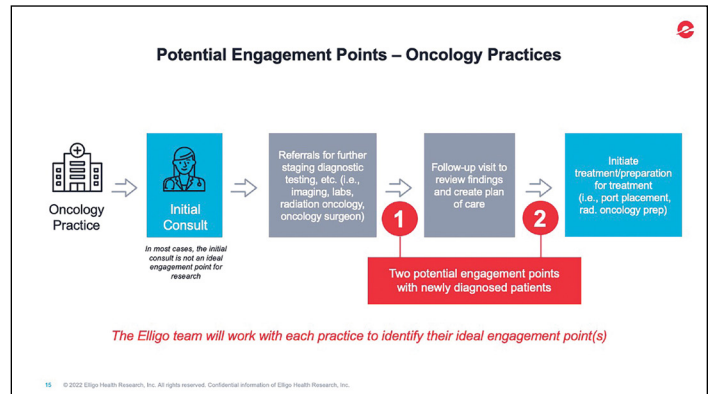
Case Study – Site Selection and Point of Care

Freenome is leveraging a multiomics platform to develop early detection tests for other cancers, beyond CRC

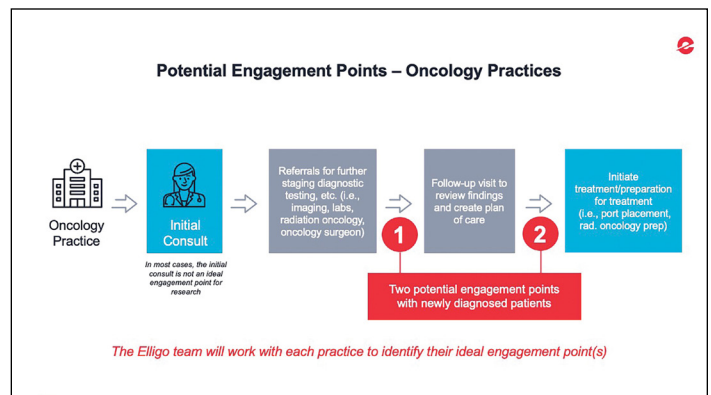
<https://www.elligohealthresearch.com/news/cerner-collaboration-to-increase-access-to-cancer-clinical-trials/>

Elligo was working with Freenome on a multi-omics platform to develop detection tests for other cancer behind CRC. They've already run their 35,000-patient trial in colorectal cancer. And we're currently working on this, what they call the Sanderson study, are working on the control arm as well as the cancer treatment arms in nine different tumor types. And what this has really taught us is that, depending on the practice, you really need to think about where these patients can be intersected with thoughts of the patient journey, what the patient's emotions are going through and where you can leverage finding these patients. I think most people default if they were running this for the first time that they want to go to oncology practices. And while they can be a great opportunity to catch these

patients, but really the better volume and the easier place to catch them is really in the step before they're referred to the oncologist.



Frequently, these patients are referred in for their initial consult, and they're already in the flow of the oncology and basically, the plan is to treat them, and they move as quickly as possible to go through the treatment because that's what the oncology practices are trying to do. Then, there are two possible potential engagement points here, but they're really far down in the process and it's a narrower window to try to catch them. You can catch them before their follow-up visits to review the findings and create the plan or right before they're initiating the treatment plan. But a lot of the times, these are times that the patients are not thinking about being part of a diagnostic trial, and are also they're very, they're much smaller windows typically than what you see. If you take a step back in



the whole process and go to the non-oncology practices, you can see where we would intersect those



patients. It's really with the initial diagnosis and the suspected malignancy. And there's a closer patient and physician relationship typically at this point. This is somebody they've been working with for a while, typically a family practice or an internal medicine physician that they've had a lot of conversations with and a lot of history. And then you can see that the patient flow goes through, and you can catch them again, you know, again, at that plan of care for follow-up. But there's a lot more time and opportunity if you're talking to these non-oncology and referral sites that are referring these patients. And it doesn't necessarily need to be just a family practice or an internal medicine practice. It can be the gastroenterologist, the pulmonologist, wherever these patients are along in their journey. Thinking about the diversity of types of sites can help enrich your population also for those control subjects, that maybe you want to have an enriched population, but also making sure that you're catching the patients from different ways that we get the tumor types and the mix that you need for your trial. And with that, I'm going to wrap up our conversation today and then open it up for any questions.

Ryan Muse

Thank you very much for this insightful presentation. I'd like to invite our audience to keep sending their questions or comments right now using the questions window for this Q&A portion of our webinar. Now, I've already received some questions. We'll get ourselves started with those. The very first question that I have for you states that, you mentioned, working with community physicians, and clinical trials of the MCD tests, what are the barriers for a community doctor being able to do so if they have not done so before?

Faith Holmes

There were actually a lot of barriers. When I was in practice, I actually tried to do it, and I was not able to, but in essence there, there wasn't somebody like Elligo around. What we

really want to try to do is leverage the fact that the physicians have the relationship with the patients that Dawn just talked about. And that's where they can concentrate, but then come in with support for all of the regulatory, the contracting the budgeting, bringing the studies to them, that a company like Elligo can do so that it will enable them because it will be a barrier for them to do it without having that logistical support behind them. But fortunately, there are solutions out there available for anyone who is interested in doing so.

Ryan Muse

That's excellent. Thank you very much for that. The next question then would like to know if patients have been compliant with current screening procedures, what can be done to improve compliance or adoption of the MCD screening tests?

Faith Holmes

I think a couple of things. One, I think the people are much more readily available or willing to have either a blood test drawn or to have some of the MCD tests that involve sputum collection. And I think those are things that patients are much more readily willing to sort of get their arms around as opposed to having to go through, for instance, you know, a bowel prep to go to get your colonoscopy or stool collection and sent the kit in, the low dose CT for lung cancer screening, that is recommended. That involves having to, you know, schedule an appointment, go in and get that done. At another time, cervical cancer screening with pap smears. I mentioned some barriers when I was talking earlier, about mammography. Some women may have an experience where they had discomfort in the mammogram, and you're just saying I'm not going to do that again. But most people who, if they're going for routine care and annual physical, oftentimes, a blood test is a routine part of what's being done. I think there's that more willingness, if that's what they have to do in order to do this screening is my thought.



Ryan Muse

That's great. Excellent. Thank you so much for that. For both of those answers. However, we have reached the end of our time here today. If we couldn't attend to your questions, though, the team at Elligo Health Research will follow up with you. Otherwise, I want to thank everyone for participating in today's webinar. You will be receiving a follow-up email from Xtalks with access to the recorded archive for this event. And so a window will be popping up on your screen as you exit. And your participation is appreciated as it will help us to improve our webinars. Now, I've also sent you a link in the chat box. And with this link, you'll be able to view the recording of this event on this page. And you can also share this link with your colleagues when they register for the recording here as well. I encourage you to do that. Now, please join me once more in thanking our speakers for their wonderful time here today. We hope that you found the webinar informative. Have a great day, everyone and thank you for coming.

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