Jason Oke
You could do 10,000 CT scans, maybe of the chest, and probably a thousand of them will have an incidental finding. Now only one or two of those are going to be something troubling like cancer and the rest are just incidental; they didn't need to be found, but they will trigger a cascade of intervention. I think the general public seems to think that cancer diagnosis is quite simple, you just need to scan people, find it and then treat it, but they really don't have any appreciation for this problem.

LuAnn Heinen
That's Dr. Jason Oke, a medical statistician and a lecturer at the University of Oxford whose work is used to help determine appropriate coverage and frequency of cancer screenings and to help us answer questions like when is more screening not better.

I'm LuAnn Heinen and this is the Business Group on Health podcast, conversations with experts on the most relevant health and well-being issues facing employers.

Today we're talking about early cancer detection, specifically tests that screen for many kinds of cancer from a single blood sample.

Hello Jason and good afternoon Oxford time.

Jason Oke
Good afternoon.

LuAnn Heinen
Thank you so much for being here today to talk about a test that potentially can detect around 50 types of cancer and at the same time identify where in the body the cancer likely originated and just from a simple blood draw and in people without symptoms. It sounds amazing and could be transformational, but there's a but. Can you tell us what's going on with this?

Jason Oke
Yes, well I can try. These new tests that some people call liquid biopsy tests, some people call them ctDNA tests, they are pretty clever things that look to find a signal in the blood that relates to cell-free DNA that would originate from a tumor, a cancer. From this with some pretty clever sequencing and then some machine learning they claim to be able to detect lots of cancers that we currently have no screening test for and also to be able to do this so we might be able to initiate treatment sooner than we would otherwise if we waited until symptoms appear. They're pretty revolutionary in that regard that they would detect cancers that we have no screening test currently. The technology is novel, there's great promise but there's a number of problems that have yet to be resolved.

LuAnn Heinen
We're going to get into that, but let's start with what makes a cancer screening test useful? How do we judge the value of a cancer screening proposition?

Jason Oke
Well I think any screening test, but particularly a cancer screening test, it needs to be simple, it needs to be safe, it needs to be precise and we need to be able to validate that. To go into more detail about precise we need the test to be reasonably sensitive so if the cancer is there, the test has a very good chance of finding it. What's really important is that it is specific for the things we're looking for, that means we don't have many false positive results. It's obviously got to be acceptable to patients so it's kind of important that it's not invasive, it's not painful, and finally we'd want it to be a reasonable cost. Then overall in the National Screening Committee, for which I was part of the research methods group for a couple of years, they have a saying which is kind of useful. They say we're looking for a screening test that has more benefits than harms and at a reasonable cost.

LuAnn Heinen
Which of those hurdles does this new multi-cancer screening detection test seem to pass?

Jason Oke
Grail's test Galleri, which is kind of at the forefront at the moment in terms of building the evidence, their test is really specific. It doesn't generate many false positives. That's great because when you invite people to screening the majority of the people do not have a cancer. You can generate false positive results in those people. It has a low false positive rate as far as we can tell from the data we've collected so far. It's less than 1 percent, so that's really really good. Now the other thing we need it to be is to be sensitive and we need it to be sensitive when the cancer is in its early stages. Now the problem at the moment is, and this has been known for quite some time, these tests are not particularly sensitive in the early stages. So the sensitivity in around sort of stage one and two, that's before the cancer is spread to the lymph nodes or distant organs, is less than 50 percent, so it's missing half of those cancers at the moment.

LuAnn Heinen
Existing tests, and there aren't very many cancer screening tests, there's four or five if you think of breast, colon, cervical, maybe PSA.

Jason Oke
In the UK we've just started a targeted screening program for lung cancer.

LuAnn Heinen
And lung cancer, exactly that's the one for certain people who are heavy smokers and are over 50.

Jason Oke
Yeah, so targeted at people at high risk, it wouldn't be offered nationally to everybody.

LuAnn Heinen
All of those tests have cleared kind of the hurdles that you just laid out, they meet those criteria?

Jason Oke
Yeah, so they've all been evaluated. In the UK we have an independent scientific advisory group that's the National Screening Committee. I was part of that for a while and I'm hoping to join that again. They advise the government, these people are kind of experts in evaluating the evidence of screening and they set a pretty high bar for what we would agree to have a national screening program for. So yeah in the UK currently only four. We're currently reviewing the evidence on prostate cancer. There's a quite a big push to initiate a prostate cancer screening program in the UK, but so far the evidence hasn't been there and namely it's the false positive and the over diagnosis problem for prostate cancer.

LuAnn Heinen
We're having the opposite problem with this particular multi-cancer screening test that we're talking about. It's so compelling also because the five tests that we currently have are screening mechanisms. The cancers that they're for account for less than 30 percent of cancer deaths in the U.S., probably the same in the UK, which means that there's no screening at all right now for 70 percent of cancer deaths.

Jason Oke
Yes, so hence the huge amount of interest in a test like this. The UK government has invested a lot of time and money in trying to get the evidence for this evaluated because it would be a leap forward. I don't think that's an overstatement, if you could screen for multiple cancers whilst keeping this false positive rate low. I think there's great interest in finding screening programs or tests, just even tests actually, for cancers like pancreatic cancer.

LuAnn Heinen
Pancreatic is one of the deadly cancers with no screening, ovary.

Jason Oke
Yes, ovarian cancer as well. That's an interesting one because we have a test. That test has been evaluated in at least one randomized trial in the UK and quite recently it failed to show any improvement in cancer specific mortality. We could probably do with a better test, but for some like pancreatic cancer which has got a pretty awful prognosis, anything could be better than what we currently have.

LuAnn Heinen
Yes, brain cancer is another one. Tell us about your role in the space designing studies and working with evidence-based medicine.

Jason Oke
Yes, aside from my previous role in the screening committee, my work in Oxford is within a research group and we're interested in cancer diagnosis through primary care rather than screening. We are principally concerned with people who present to their GP with signs and symptoms of cancer and we're looking of ways to improve the way that happens. Historically the UK has kind of seemed to be lagging behind other western countries and probably the U.S. in terms of measures such as survival and so there's been a number of initiatives in the UK to try and improve this. One of the ways we think this can be done is by diagnosing cancer sooner and getting people referred and treated earlier. A lot of the work I've been involved in in the last 10 years has been evaluating the use of cancer tests and more recently we've completed one study with the Galleri test used in people who present to the GP with what we call vague symptoms of cancer, so this could be something like weight loss. We could show in that study it was a kind of clinical validation study because you could show the test is as accurate as it was claimed in that particular population. We couldn't assess whether it improved patient outcomes and we're planning a study in that where we might be able to speed up the diagnosis for a range of different cancers. So it's really exciting being involved in that and we're hoping that this continues.

LuAnn Heinen
So the Grails Galleri test is the one that is the most studied. My understanding is that the only randomized controlled trial on this kind of test, this liquid biopsy multi-cancer detection test, the Galleri is the leading example of the first randomized controlled trial was conducted in the UK and results were very recently released. It's fresh.

Jason Oke
Yeah, I was part of the screening committee. We were looking very closely at that trial because we knew how important it was. We were involved in negotiations to how we might extend some of that trial. Yeah, you're right, enrolled something like 140,000 people from the general population in England between 50 and 77. These are people without symptoms, so they are otherwise healthy and not being investigated for cancer. I think they invited over a million people to this study. This is an expensive study, 100 plus, 100 million pounds to run this. It will carry on for probably six years. They randomized, you got put into two groups, you had blood taken and then randomized as to whether that blood would be sent off to California and evaluated by Galleri or the blood was just stored and not acted on and people who in which there was a cancer signal detected, then randomization was unblinded and they would have then gone through the normal channels in the UK referred to a cancer specialist. Grail released their first results. Their primary endpoint was a reduction in stage three and four cancers, so that was a kind of composite outcome. Late stage cancer reduction in late stage cancer and that was not significant so it was a kind of negative result in terms of the primary outcome. Now their secondary outcome which was a reduction of stage four according to the company themselves because they've been a little bit cagey maybe about the results at the moment, we haven't seen all the data. They think that's really quite encouraging that they've reduced stage four incidents. Now given that the results they kind of seem a bit conflicting I think we could surmise that the reduction in stage four means that most of them have probably gone to stage three so hence no difference between three, four, and one, two. What they would really like obviously is changing people's diagnosis at stage four to one and two, but they weren't able to show that.

LuAnn Heinen
Yes, and there was some pretty harsh commentary here in the U.S. saying clearly failed this trial, but all the signals as you've kind of suggested it doesn't seem this is the end of the story. There's a lot of ongoing research, there's just too much potential here, I think it doesn't seem like a derailment.

Jason Oke
No, I don't think so. I think it's disappointing even that stage reduction is really only a surrogate. What we'd really like to demonstrate is an improvement in patient outcomes. I mentioned this ovarian trial that we did in the UK a number of years ago and they did reduce stage four presentation of ovarian cancer in stage

four and they were able to do that and show that in the trial, but actually it didn't lead to a statistically significant reduction in cancer specific mortality. So you can sometimes produce a stage shift but actually it doesn't necessarily impact on the outcome that we would really like to affect, which is obviously the most important outcome, cancer specific mortality.

LuAnn Heinen
Then that brings up cost effectiveness of something like this.

Jason Oke
Yes, we're all very well aware this is an expensive test at the moment. I think it's a thousand dollars in the UK, that's about 700 to 800 pounds. This is a very expensive test and so if you wanted to roll this out to millions of people, that's not cheap and it's probably only likely to bring benefit to a small number of people. It would have to be cost effective. The other thing that we've got logistical concerns about, the logistics at the moment in our trial because we have to send it to California wait three weeks for the test result to come back. That's a kind of an additional consideration. Cost is part of that, but some of it's just about the setup as it currently is. The UK government was kind of almost promised to buy many more of these tests and then Grail would then set up a lab in the UK and that might change the cost effectiveness, but this is all kind of hypothetical at the moment.

LuAnn Heinen
We're in kind of an interesting gray zone because these tests are commercially available. A provider has to order them. They're not approved by regulatory bodies, either NHS I guess it would be in the UK, and not by the FDA here, so that puts clinicians and consumers in an interesting space. Let's discuss the consumer perspective. This is really quite interesting. Have you seen the Super Bowl ad that ran here in the U.S. for Hims and Hers? I want to get your reaction to it, but first let me fill in people who might have missed it or if you watch the Super Bowl you'll remember. It was a very provocative ad and here I'm going to do my best without the music or the video or the drama, but the message is rich people live longer, all that money doesn't just buy more stuff, it buys time. The wealth gap is a health gap, and my aside is we can agree they're not wrong, and the ad pitches “the same science, the same access, no connections required,” and it mentions early cancer detection, among some of the other offerings. What was your reaction to that?

Jason Oke
Well, it's a clever ad in some ways. Clever but slightly devious, I would say. It's playing on a kind of division in people, rich versus poor. It reminds me possibly of the mistakes that been made in the past about cause and effect. I was kind of rereading a book on screening this morning and they were talking about how screening really came about. It was really from life insurance where people running life insurance companies wouldn't offer a life insurance without a medical examination and then they realized well maybe we could offer medical examinations more frequently to people, so they started doing that. Then they started to look at the life expectancy of these people who had regular medical examinations and they were living longer than what they projected and they deduced from that that it must mean that the medical examinations are causing people to live longer. It's not correct. It's probably the other way around and this has got a name. This is called healthy screenee bias. So if you offer screening and you do these in randomized trials you offer people screening, they don't have to accept the invitation. What you see and you can see in trials is that the people who accept the invitation are generally healthier. Sometimes you can see a difference in life expectancy. It's got nothing to do with what's been offered in terms of screening. They are just healthier because people who attend screening regularly just tend to do other things that are more healthier for them. Some of these things they're pitching is possibly misleading.

LuAnn Heinen
Your comment about life insurance companies brought us this, I’m pretty sure they're the ones we have to thank for the concept of the BMI, the healthy height and weight measures too all came from their business model. Let's say if you're an employer and you've got, you know lots of employees who could be interested in this test, you're not going to cover it at this point, but is there any guidance either pro or con or over a certain age that it might make sense for people who want to self-pay.

Jason Oke
Rather than say definitely do not do this or use this, I'd like to think we could give them the information they could make an informed choice. For some people it might help them a lot if they're particularly anxious. Maybe if they've got a family history of cancer and I wouldn't want to stop people doing something of their own free will whether a government or a country decides to offer something to people. That's a different proposition in my eyes. If people want to spend their money, their hard-earned money on this, I think the best we can do is to try and present the evidence and try and explain to them there are possible downsides other than the financial costs. We tried to present the data and the evidence in the most balanced way we possibly can.

LuAnn Heinen
From a U.S. large self-insured employer perspective, because the specificity is so high and there are very few false alarms, you said under 1 percent, it's not likely to cause lots of rounds of testing and expense for the self-insured employer. Would you agree with that?

Jason Oke
Yes, I mean as far as we know at the moment the false positive problem is small and that's really important offer if you're going to offer a test to hundreds of thousands of people that really matters, because you don't want your health services to be overburdened with people. What we don't know, I think as yet, is whether it tends to find cancers that are not clinically significant. Now other screening tests have this problem. Mammography, PSA, to some extent thyroid, they have a problem that they can find cancers that look like they've been caught at an early stage, but actually probably would never go on to cause people problems. So we don't know enough about these tests yet. There's some positive signals though about that because they don't tend to be as sensitive for the kinds of cancers that are prone to over diagnosis. In our study in the UK it was particularly poor at finding prostate cancer. That sounds odd to say, but that's not necessarily a bad thing. Prostate cancer is often over diagnosed, but we don't know for sure. It could be these tests are actually better at that than our existing screening tests.

LuAnn Heinen
Well while we're on the consumer topic, there is an alternative, full body MRI scanning to detect cancer and that is on full offer here in the U.S. to patients who can afford to pay. That's probably three times the cost of the multi-cancer detection test, so it's maybe around three thousand dollars. Where do you think that fits into the picture?

Jason Oke
Well these have obviously been around, full body MRI, full body CT, they've been around for longer and I think we kind of understand where the problems lie. Certainly as you get older, maybe less so for younger people, but when you start using these really kind of advanced imaging technologies that are able to look in great detail at the body, you start to find things that maybe were never going to be a problem. You could do 10 000CT scans, maybe of the chest, and probably a thousand of them will have an incidental finding. Now only one or two of those are going to be something troubling like cancer and the rest are just incidental. They didn't need to be found, but they will trigger a cascade of interventions. I think the general public seems to think that cancer diagnosis is quite simple, you just need to scan people, find it, and then treat it, but they really don't have any appreciation for this problem. Obviously clinicians, radiologists, know this problem very well and that's why they would be reluctant to offer this. I think there may be something you can do with it. Again, for people who had vague symptoms of cancer, we offered them kind of quick direct access to a full-body CT, but that was done in a very regulated way. We're talking about that spot in the lung that you know in a 50-year-old ex-smoker is that cancer will actually probably very unlikely to be cancer even in a smoker. What will happen there, probably more CTs for 6 to 18 months to try and work out whether it's moving and in the meantime that's a lot of anxiety for someone. You find that because maybe they broke a rib they had a CT and then they find this thing that's not related to anything else. Once you've found it, you can't just ignore it. That's the problem and it's unlikely statistically you found something that would go on to cause a major problem. It's much more likely that this is nothing and so those extra tests, they give you radiation CT, MRI not so much, but there's all kinds of expense and anxiety problems and then just overloading the health system, which is I think probably most health systems are close to full capacity.

LuAnn Heinen
You've used the word over diagnosis a couple of times. That means finding cancers, like something in the prostate that's never going to amount to anything, is that the extent of it or is over diagnosis have a broader meaning?

Jason Oke
It does have a broader meaning. It's much easier to think of it in terms of cancer in my opinion, because that's where that term originated. We can provide a clear definition of that. It would be something that meets the definition of cancer in terms of pathology and histology and stuff, but it isn't a cancer that will grow and cause symptoms and eventually lead to death or you would never have found it without a screening test. We know that occurs in things like prostate cancer for a number of different reasons. Now you can apply the same concept to all kinds of different medical conditions.

LuAnn Heinen
Very interesting. One of the things that the National Cancer Institute has an article about is how many doctors aren't fully able to interpret cancer screening statistics. The Cancer Institute's point is that screening is only a good thing to do if it advances the time of diagnosis and earlier treatment is more effective than later treatment. Earlier treatment can do something I think was the point and that a lot of physicians get hung up statistically on looking at five-year survival rates that seem better for people who are screened, but actually there's no impact on mortality.

Jason Oke
Yeah, I teach these subjects to different groups of people in the university. I really enjoy them, but they are difficult concepts for people to understand, even people in the medical profession. I remember a survey they did in the U.S. probably 20 years ago now. They asked clinicians, about 200 odd clinicians, what constituted evidence that screening was effective and one of the questions was if five-year survival is higher in people screened compared to people not screened, is that proof that screening is working. The majority of people who answered in the survey, who are health professionals, said yes it did.

LuAnn Heinen
I read that 68 percent.

Jason Oke
Yes, I can't remember the exact number. So realizing that then they haven't fully grasped the problem that this thing called lead time bias. Now people who are involved in research and screening research will know this very well that screening has to advance the time of diagnosis. It has to otherwise it has no use utility at all. It will add survival time even if it makes no impact on the eventual outcome. The lead time is that concept of how much earlier does the screening test detect your condition. If you can imagine a hypothetical situation where your symptoms would have appeared and you would have gone to the doctor and you had a screening test instead, maybe that was two years before symptoms would have appeared, that's your lead time. You've instantly added two years survival to your trajectory, but it may mean nothing at all. We know we can't compare screening in terms of survival. That mistake is commonly made. It's very similar to the problem I'd said earlier about healthy screening bias. People who attend screening, they are generally healthier and they also seem to survive cancer longer as well if it's detected in screening. There are those problems, but there's other problems as well. There's length time bias, that screening tends to find the slow growing cancers and miss the quick cancers. Again, that gives screening an advantage which is unfair. It's not really a balanced comparison and the biggest one really is the problem of over diagnosis because people who've got an over diagnosed cancer have a very long survival time. If you add those people into the population statistics, it makes the overall five-year survival go up. We've seen that in prostate cancer in the UK when they started using PSA in primary care, which we sometimes called opportunistic screening. Incidents of prostate cancer went up threefold. That's exactly what we'd expect, because there's lots of prostate cancer out there that could be found if we had a suitable test or a test that was able to find it. The incidents went up and the survivor went up as well, but most of that is artificial. Maybe a better example was from the days when Rudy Giuliani was Mayor of New York. I think he was diagnosed with prostate cancer and he'd said he was glad that he wasn't diagnosed with that in the UK because when you compare survival between the U.S. and the UK, the survival in the U.S. is about 90 percent five-year survival and in the UK it was about 40 percent. He wasn't wrong. They were the statistics,

but actually if you looked at the mortality rate between the two countries, they were pretty much the same. What had happened in the U.S. is they'd started to over diagnose prostate cancer. That had inflated the survival and we know that, we understand that, but people such as the mayor did not get that point. So was his prostate cancer ever going to kill him, maybe not.

LuAnn Heinen
Talk a little bit about maybe what you see as the future trajectory of cancer screening, the lab science behind this new category or not so new. Maybe last five years or so this category of liquid biopsies is remarkable. The ability to find tumor DNA in our blood, tie it to a certain kind of cancer, and this unfulfilled still promise of detecting deadly cancers that don't have any kind of screening. But then we're also in a climate where there seems to be a little bit of a trend toward less cancer screening, because of an evolving understanding that more screening doesn't necessarily mean fewer cancer deaths and although in the UK you said that prostate cancer screening is maybe back on the radar. While clinical trials have shown that cervical, colorectal, breast, and lung cancer screening can save lives, the amount of benefit is, as the National Cancer Institute puts it is, “misunderstood” and that the number of people who need to be screened to save one life is much larger than we generally understand.

Jason Oke
Yes, there's the public perception of what screening can do and then there's the reality. I think people's perception is that screening would solve all problems. From all the examples, we know that's not true. It's not just as simple as diagnosing cancer earlier. We can see that now in lung and breast and colorectal. I think in breast cancer we might reduce mortality by 20 percent, but that still means lots of people will still die from their breast cancer even if we're diagnosing it earlier. So we kind of know from the evidence that it's not that simple, but a lot of push for screening comes from a misunderstanding. But also because obviously it's a scary condition. Probably everybody knows someone who's gone through that. We would like to avoid it and if we think it's as simple as just having a test every other year and that will get us out of the problem then you could see why we would want to do everything we can to make that happen.

LuAnn Heinen
We haven't had much development of new single cancer screening tests in a really long time. The same few four or five tests have been around for a long time and we've sequenced the human genome, we're editing genes. We have that capability. Immunotherapy for cancer treatment is really growing, progressing. AI capability can read imaging and detect cancer. We want to believe, we want to think that this multi-cancer detection test from blood to detect cancers early that there's hope there, it needs some tweaking it sounds like.

Jason Oke
Yes, it needs some tweaking. I'm fairly in the middle. It's novel. In my experience there really isn't anything else that you can draw a small amount of blood and then it might be able to say you've got a cancer and we can pinpoint all or at least point to where it is in the body. That really is quite novel and there's nothing else really like that up to now. It would be great in a way because also, again, it would be easy to do if we can make it cheaper, but a blood draw I think is more appealing for most people than getting a stool sample. People don't like doing that and that's reflected in the uptake of screening. I've never had one myself but a mammogram is not particularly a pleasant experience.

LuAnn Heinen
Not comfortable.

Jason Oke
Yes, avoiding that would be great. I think for most people blood draw is fairly simple. It does offer a lot of promise, but we shouldn't underestimate just how difficult the challenge is. Even if you've got a great test, cancer seems to be such a challenging disease.

LuAnn Heinen
A wily foe.

Jason Oke
Yes, exactly. Personally I don't think it's just as simple as diagnosing it earlier. I think it's a much harder nut to crack. My own thought would be that we would solve this either from prevention probably, and we can do that for some cancers and maybe that will change over time, but also that we'd get better at treatment. Whether we ever can fully combat this problem, but it needs to be more than just earlier diagnosis. I think prevention and treatment we need similar amounts of investment in those two areas as well. Wouldn't it be great if someone could say, well all right your cancer it's quite well developed, but actually take this course of treatment for two weeks and it'll be gone, like an antibiotic equivalent. Perhaps it's pie in the sky thinking, but we need all three probably.

LuAnn Heinen
All three being prevention, screening, and …

Jason Oke
Really good treatment, and as you said, there's been some really good advances in treatment as well. All three would be great.

LuAnn Heinen
Thank you so much, Jason, for this conversation.

Jason Oke
Well, thank you for inviting me and it's been a pleasure to talk about this subject with you.

LuAnn Heinen
I've been speaking with Dr Jason Oke about multi-cancer detection from a blood sample and what failing a major clinical trial means for this still potentially promising screening tool.

I'm LuAnn Heinen and this podcast is produced by Business Group on Health, with Connected Social Media. If you like the episode, please rate us and leave a review.