

Transcript of Hari Shroff, Ph.D.

Date: February 4, 2025
Case: Bruker Spatial Biology -v- President and Fellows of Harvard College (PTAB)

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WORLDWIDE COURT REPORTING & LITIGATION TECHNOLOGY

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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BRUKER SPATIAL BIOLOGY, INC.,

Petitioner,

v.

PRESIDENT AND FELLOWS OF HARVARD COLLEGE AND 10X GENOMICS,

Patent Owner.

_____

Case IPR2024-00526

U.S. Patent No. 11,542,554

_____

Deposition of HARI SHROFF, PH.D.

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Pursuant to notice, before Judith E. Bellinger, Registered Professional Reporter, Certified Realtime Reporter, and Notary Public in and for the District of Columbia.

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P R O C E E D I N G S

HARI SHROFF, PH.D.,

Being first duly sworn, was examined and testified as follows:

EXAMINATION BY COUNSEL FOR THE PETITIONER

BY MR. WALTER:

Q Good morning, sir. Could you, please, state your name and address for the record.

A Sure. My name is Hari Shroff. My address 19709 Gap Junction Lane, Ashburn, Virginia, 20147.

Q I'm going to go over a few basic rules related to the deposition before we get started.

First, you understand that in response to my questions, you need to answer truthfully?

A Yes, I do.

Q You understand that your counsel may object, from time to time, to some of my questions?

A Yes, I do.

Q And you understand that you still need to answer unless you're instructed not to answer

for reasons related to privilege?

A Yes.

Q Now, you understand we have a court reporter taking things down?

A Yes.

Q So, what I want you to do is do your best to make sure that we don't talk over each other.

Do you understand that?

A Yes.

Q In particular, what I'd ask that you do is you let me finish my question before you begin your answer.

Do you understand that?

A Yes.

Q Have you ever been deposed before?

A I have not, sir.

Q Have you ever served as an expert witness before?

A I have not.

Q What did you do to prepare for your deposition today?

A Sir, I met with the law firm Sterne Kessler, including those seated in the room. I've reviewed literature relevant to the case, as described in the bibliography of my declaration. Yeah, that's what I did to prepare.

Q You said you met with the attorneys of Sterne Kessler.

When did you meet with those attorneys?

A Most recently, I met with them over the last few days. But also over a period of a few months, over Zoom, sir.

Q Solely for this deposition?

A Solely for this deposition.

Q So you said you met with them over the last few days. How much time did you spend with the attorneys from Sterne Kessler yesterday?

A On the order of about seven or eight hours.

Q Did you meet with them on Sunday as well?

A I did.

Q And how long did you spend with them on

Sunday?

A Roughly, the same time, sir.

Q And did you meet with them on Saturday?

A I did not meet with them on Saturday.

Q How many hours did you spend with them on Zoom to prepare for your deposition?

A On the order of 10 hours or so.

Q So you probably spent on the order of 25 hours preparing for your deposition?

A More than that, sir. Because of the time that I spent reviewing the literature on my own.

Q Okay. How much time did you spend -- strike that.

How much time do you think you spent reviewing the literature on your own to prepare for this deposition today?

A I would say, roughly, the same amount of time, 20 to 30 hours in total.

Q So, for this deposition, you've probably spent somewhere over 50 hours to prepare; is that right?

A That's about right, sir, yes.
Q I'm going to mark as -- well, I'm -- actually, I'm not going to mark the exhibit, it's already marked.
(10x Genomics Exhibit 2024 previously marked for identification and retained by counsel.)
Q I'm going to hand you a copy of what's been previously marked as Exhibit 2024.
This is the declaration that you prepared for this IPR proceeding?
A Yes, it is, sir.
Q And do you have an estimate of, roughly, how much time you spent preparing this declaration?
A I would say, together with the lawyers, on the order of, maybe, 20 hours, something like that. Including the time, of course, spent on Zoom and including the time spent reviewing the literature, sir.
Q Okay. Now, you've also brought with you a document here today. Is that just a copy of

your declaration?

A Yes, it is, sir.

Q Okay. That's fine.

I want to ask you a few questions about the documents you reviewed to prepare for the deposition today.

Did you review the declaration of Dr. Kirk Czymmek?

A Yes, I did, sir.

Q You reviewed that in preparing for your deposition in this case as well?

A That's correct.

Q Now, is there anything in this declaration that -- and when I say "this declaration," I mean Exhibit 2024, your declaration.

You reviewed that before coming here today to testify, right?

A Yes.

Q So you're deeply familiar with your declaration?

A Yes.

Q Is there anything in this declaration you want to change?
A No, sir.
Q Is there anything from this declaration you omitted?
A No, sir.
Q This is a complete statement of your opinions in this case?
A This is a complete statement of my opinions in this case.
(NanoString Exhibit 1001 previously marked for identification and retained by counsel.)
Q Now, I assume that another document you would have reviewed in this case is the patent that's at issue, which is the '554 patent?
A That's correct, sir.
Q Let's get that out so I'll have that in front of us.
You're familiar with the '554 patent.
A Yes, I am, sir.
Q Now, you're aware that there was a

decision by the board which we also sometimes called the PTAB to institute review in this case.

Are you aware of that?

A Sir, if you're referring to the information on paragraphs 57 and 58 of my declaration the '554 patent's prosecution history, then I am familiar with that as described in my declaration.

Q No, I think I'm asking about something else.

Are you aware that in the IPR proceeding, one of the things the board does, as a threshold matter, is make a decision on whether to institute the IPR?

A The board? The patent board?

Q That's right. Sometimes called the PTAB.

A Yes, I believe so.

Q Did you review the board's institution decision in this case?

A Which document are you referring to specifically, sir? It would help me out if you

could tell me which of the exhibit numbers we're discussing.

Q Well, you know, I honestly don't know if it's an exhibit to your declaration. I'm just asking if you reviewed the board's institution decision in this case?

Do you know what I'm referring to when I say "the board's institution decision"?

A I'm not exactly sure what, precisely, you're referring to there, sir.

Q Okay. Let's go to paragraph 49 of your declaration.

A Paragraph 49 of my declaration, sir?

Q That's right.

Here you cite some patent applications that you say are related to -- that you state are directed to MERFISH that were filed for by the group that prepared the Chen publication.

Do you see that?

A Yes, I do.

Q Okay. And what is your basis for your assertion that those patent applications -- let me

ask this question first: Did you review those patent applications in this case?

A I certainly reviewed the portions of those patent applications that I cite here, sir, on pages 44, 45, and 46 of my declaration.

Q Okay. And what is your basis for your assertion that those patent applications, that you discuss, are directed to MERFISH?

A Well, sir, the material on page 44 directly discusses multiplexing an error-robust coding schemes, which refer directly to MERFISH. Furthermore, in the same paragraph, they discuss prior art, naming Lubeck and Cai, and they also discuss Chen, combinatorial labeling with error-robust encoding schemes, which I believe is MERFISH, sir.

(Exhibit 1073 marked for identification and attached to the transcript.)

Q Okay. I've handed you a document. We're actually going to mark this document.

MR. WALTER: Let's mark this as 1073.

Q Okay. I've handed you a document that

we've marked as Exhibit 1073, it's U.S. Patent Number 12,209,237.

And if you could take a look at item number 21 on the first page.

A For the record, I would like to state that I've never seen this document before. It's not cited in my declaration and I've never seen it before, so...

Q Well, let's slow down a little bit.

A Okay. We can explore it. But for sure I've never seen this before.

Q Let's be sure about it.

A I am sure about it. The date of the patent is January 28th, 2025.

Q Let's take a look at item 21 on the first page.

A Item 21 on the first page. We're talking about this page?

Q Yes.

A Item 21, yes, I see something called item 21, yes, sir.

Q You see it says application number

17/374,000?

A I do see that.

Q Okay. Now, if you take a look at paragraph 49 of your declaration.

A Yes.

Q That's the patent application you reviewed in connection with paragraph 49.

A Application number 17/374,000 is the -- yes, that part is correct.

Q Okay. Now, why did you review these patent applications from the Chen group that are directed to MERFISH?

MR. HOLMAN: I just want to caution the witness not to discuss the substance of communications with counsel. Aside from that, you can answer.

Q Yeah, I'm not asking -- I'm not asking you to reveal the substance of communications with counsel. What I'm asking is, why you believed these patent applications from the Chen group, that are directed to MERFISH, were relevant to your opinions in this case?

A One of the central arguments in my declaration, sir, is that Dr. Czymmek is claiming that by combining Chen, Shen and Cai, one could get to the claims of the '554 patent. But one of my arguments, sir, is that a person skilled in the art would not have combined these applications. And the reason for that is that the Chen paper, the MERFISH paper, the goal of that paper is to increase the multiplexing, increasing the throughput of MERFISH. It has nothing to do with 3D MERFISH. And so, in that context, in my declaration, what you're seeing on pages 44, 45, and 46, has to do with the discussion of increasing multiplexity in MERFISH.

Q Are you saying that you believe these patent applications from the Chen group, that are directed to MERFISH, are helpful for someone skilled in the art to understand how MERFISH would be used?

A What I'm saying, sir, is exactly what I state on page 44 of my declaration. That by reviewing portions of these file histories, the

research group, i.e., Chen Zhuang, acknowledge the limitations of multiplicity of single-molecule FISH and SeqFISH prior art, prior to MERFISH. That's exactly what I'm saying.

Q Is it your view that someone skilled in the art, looking at these patent applications, would have an understanding of what the intended purposes of MERFISH were?

MR. HOLMAN: Objection. Form.

Q Let me ask the question a little differently. Is it your testimony that someone of skill in the art looking at these patent applications that are directed to MERFISH would do so to help get a better understanding of what the intended uses of MERFISH were?

A Well, I'm sorry, can you say the question one more time.

Q Is it your understanding that these patent applications that are directed to MERFISH are relevant to help a person of ordinary skill in the art understand what the intended uses of MERFISH were?

A The reason I cited these patent applications, sir, is that I'm trying to make an argument that MERFISH is directed towards multiplexity. That's the sense in which I'm using these additional documents, as I describe in my declaration.

Q Okay. So --

A And I'd like to furthermore state that the -- exactly as I say in paragraph 49, these are -- these are documents that help support the idea that in 2016, the same group was directed towards drastically increasing the throughput of a procedure.

So after 2015, after the date of the '554 patent, the point is that the MERFISH group were, themselves, interested in going after multiplexing. That's the context in which these paragraphs should be read and the context in which I cite these documents.

Q Okay. So is it accurate, then, that you cited these patent applications directed towards MERFISH because they helped you understand

what MERFISH was directed towards?

A Well, sir, I understand what MERFISH was directed for. But these documents further support my assertion in this declaration that the goal of MERFISH is increase multiplexing in RNA FISH applications.

Q Okay. Is it fair, then, that you believe these patent applications, that are directed towards MERFISH, reflect evidence of what the goal of MERFISH is?

A Of course. These patent applications, the ones that I am citing here, are examples after 2015. So in that sense, you know, it's happening after the date of the '554 patent, but it's certainly consistent with the idea that this group and the field, in general, was moving towards increased multiplexing.

Q I was asking something more general.

Is it fair, then, that you believe these patent applications directed towards MERFISH reflect evidence on what the goal of MERFISH was?

Is that fair?

MR. HOLMAN: Objection. Form.

A I think what I would definitively say is that, as I say in this declaration, the parts of these applications that are relevant are discussing, specifically, the advance of MERFISH over prior art vis- -vis multiplexing. That's what I'm saying.

So exactly as I say, Chen demonstrates multiplexing requires an error-robust encoding scheme. And the previous methods fail to disclose or are inadequate for this purpose. So these patent applications, exactly as I state here, are supporting that assertion.

Q Okay. You rely upon these patent applications to help understand what the goal of MERFISH is, fair?

A These patent applications help support what I already understood the goal of MERFISH was, which is an advance in multiplexing over the prior art.

Q Did you identify any other goals of MERFISH in reviewing these patent applications

from the Chen group?

A The patent applications and the relevance of them, are relevant only insofar as what I describe in these -- in this declaration, namely, the advance of MERFISH in multiplexity over the prior art.

As I've said before, I don't recognize this document as it's dated after the relevant dates in this declaration and it's not in my bibliography.

Q Okay. Now these documents -- you do agree this is the same application that you cite in your patent, right -- cite in your declaration, right?

A I certainly agree that this line is the same, sir.

Q Okay. Now, the passages that you cite on paragraph 49 and 50 of your declaration.

A Pages 49 and 50?

Q Paragraphs 49 and 50.

A I'm sorry, paragraphs 49 and 50, yes, sir.

Q Do you know if those passages were generated before or after the priority date of the '554 patent?

A Well, I think I can definitively answer that statement if you provided me with these documents, sir, but I'm not -- I don't readily have the exact date of either of these documents in hand.

Q Again, I'm not asking for the exact date, I'm just asking whether you know if it's before or after the priority date?

A Of all these documents, I can't say for sure, sir.

Q Okay. Now, it states on page 49 that you reviewed portions of the file histories.

A Page 49, sir?

Q Paragraph 49.

A Paragraph 49.

Q I'm going to make that mistake multiple times. And you don't have to call me sir.

I understand, from reviewing portions of file histories of U.S. Patent Application

Number 17/374,000 and 18/184,967.

Do you see that sentence in paragraph 49?

A I do.

Q Now, first, there's something there called a file history.

A Uh-huh.

Q Do you know what a file history is?

A I believe so, sir, yes.

Q What is your understanding of what the file history is?

A So, for example, there could be previous iterations of the patent or previous history relevant to the patent, the final patent. That would be referred to as the file history.

Q When you say there could be previous iterations of the patent, what do you mean by that?

A Well, a research group could, for example, file for a patent, and then that patent could be contested or there could be additions to the patent. So, for example, if you look at this

date, 2025, that's a very recent date in history. It's very likely that the ideas in this example originated before this date and these disclosures would be displayed in the file history of that patent.

Q So your understanding is the file history is the record of material that comes before someone files for a patent?

A I wouldn't say it quite like that, sir. It could be, for example, a history, you know, prior to this date, right? So the -- this is marked the date of the patent, but there could be previous disclosures relevant to this date that would be encompassed in the file history.

Q Do you know for sure whether that's part of the file history or not?

A I think that is part of the file history.

Q Do you know?

A I'm not a hundred percent sure.

Q Okay. And just so we're clear, the date you were referring to was the January 28th,

2025 date, on Exhibit 1073?

A This was an example, again, on the patent -- on a document I had never seen before. It was merely an example.

Q I just want to make sure the record's clear. The date you were referring to was that January 28th, 2025 date, right?

A The date I was referring to in an example, on a document that I've never seen before, is, indeed, January 28th, 2025. Again, just for clarity.

Q Okay. Now, you talked earlier about how you looked at documents related to the patent applications that the Chen group filed that were directed towards MERFISH. And in paragraphs 49 and 50, you discuss some aspects of the prosecution history.

Do you know what's more important and more relevant towards understanding the goal of MERFISH, is it the prosecution history of that patent application or the actual specification of the patent application?

MR. HOLMAN: Objection. Form.

A That's a very general question, sir, that I don't quite know how to answer. The goal of MERFISH is clear from the paper that MERFISH was published in, which I reviewed thoroughly.

I won't speculate about this document and the goal of this document or some other document. The goal of MERFISH is very clearly outlined in the MERFISH paper, in the abstract of that paper.

Q I was asking something different, okay? I was asking whether for this application, U.S. Patent Application Number 17/374,000, what, in your understanding, is most relevant, if you want to get an understanding of what MERFISH is directed to? Is it the specification of that application or is it the prosecution history?

Do you know?

MR. HOLMAN: Objection. Form.

A Sir, I can't answer that question in any the detail. I'm not a lawyer. But I certainly can't answer that question without

reviewing this exact document.

Q And this exact document that you're referring to is U.S. Patent Application Number 17/374,000?

A Well, I guess, specifically, what's relevant here is the portion of the file history which I cite in this document. Which, again, as I think I've said before, is relevant insofar as it bolsters the idea of the goal of MERFISH. But the goal of MERFISH, vis- -vis increasing multiplexity, is obvious from the document, the paper that was published by Chen and Drum.

Q Okay. I wasn't asking -- I was just asking something really simple. In your last answer, you said you couldn't answer a question without referring to this exact document. What did you mean when you were saying "this exact document"?

A The portion of the file history of U.S. patent application that I cite here.

Q Oh, so you didn't review the file history that you cite in your declaration?

A I reviewed the file history, of course not word for word, but the relevant part of the file history in question is what I state here, sir.

Q Okay. Did you review U.S. Patent Application Number 17/374,000?

A Portions of its file history, sir, as described here.

Q But you did not review the application itself?

A As I say here, I reviewed portions of the file history from this application.

Q Why didn't you review the application itself?

MR. HOLMAN: Objection. Relevance.

A Well, the documents that I consider relevant for this declaration are included here in this bibliography, sir.

Q So you helped select those documents?

A It's true to say that I helped select the documents, yes.

Q And you told the attorneys, I want to

see the prosecution history but not the application? Is that what you told the attorneys?

MR. HOLMAN: Objection. Form.

A Honestly, I can't recall, sir.

Q Who made the decision to not have you review the application itself?

MR. HOLMAN: Objection. Going into the substance of communications with counsel. Objecting on the basis of privilege.

Instructing the witness not to answer.

Q Let me ask the question this way: Did you make the decision independently of the attorneys to not review U.S. application number 17/374,000?

A Honestly, I can't recall, sir. About what I -- whether I did or did not review -- ask to review this particular file portion. I just cannot remember.

Q One thing we know is clear. You do believe that at least a portion of the prosecution history of U.S. Patent Application Number 17/374,000 is relevant to understanding what the

goal of MERFISH is, right?

A What I would say, sir, is exactly what I say in the first sentence of paragraph 49. The objective of increasing multiplexity in MERFISH is further demonstrated by the research group's later publication in patent applications directed to MERFISH.

In other words, a POSA reading the MERFISH paper would have understood what the goal of MERFISH was, that is increasing the throughput, increasing the multiplexity of single-module FISH elements.

Q I'm not trying to say this is the only thing. I never said that.

But what I want to confirm is that you do believe that portions of the prosecution history for 17/374,000 is something that would help someone understand what the goal of MERFISH is, right?

A And as I said, the goal of MERFISH is clear from the paper alone. As I say, exactly as I say in this declaration, this -- the material in

paragraph 49 is helpful insofar as further demonstrating where they were going and the goal. But the goal is clear from the MERFISH paper.

Q Okay. What investigation did you do, if any, with regard to these prosecution history and patent applications to help understand if there were any other goals or any other potential uses of MERFISH, besides increasing multiplexity?

A Sir, I only reviewed these patents insofar as they bolster my core argument here, which is that the goal of MERFISH is increasing multiplexity and the cited information in this document further bolsters that case.

Q Okay. In preparing your declaration in this case, did you review any marketing documents related to the Xenium or CosMx products?

A Can you clarify what you mean by "marketing documents," sir?

Q Advertising material that either 10x or Bruker provided their customers.

A Sir, the documents that I reviewed, in the context of Xenium and CosMx, are described in

my declaration, and I use them insofar as I discussed the use of objective indicia, confirming the nonobviousness of the '554 patent.

So, the exact literature that I reviewed are shown in pages 103, 104, 106, 108, and there are references, in my declaration, additionally, to the exhibit numbers, which you'll find in my bibliography. For example, Exhibit 2064.

Q Are there any documents you reviewed that you would characterize as marketing or advertising literature related to Xenium or CosMx, that you can recall?

A The list of documents are 2060 through 2071, as illustrated in my bibliography. These include user guides, manuals, grant support documents. There's a press release, 2070, and there's information from the website, 2071.

Q Would you characterize any of those things as marketing, advertising, or promotional material?

A Not that I can recall, sir.

Q Okay. Did you talk to any of the 10x or NanoString marketing personnel regarding how they market the CosMx or Xenium product?

A I did not talk to any representatives from those companies, sir.

Q Do you have any experience in marketing of instrumentation for spatial genomics?

MR. HOLMAN: Objection. Relevance.

A I have no experience marketing spatial genomics literatures, no.

Q Instrumentation, not literature.

A Oh.

MR. HOLMAN: Objection. Relevance.

A I have no experience marketing instrumentation for spatial genomics.

Q Do you know what features Xenium 10x emphasizes in its sales efforts?

A I do not know what features Xenium advertise in their sales records. What I do know are the figures and the literature cited in my declaration that tie these products to the elements of claim 36 in the '554 patent, sir.

Q Okay. Do you know what features of CosMx Bruker emphasizes in its sales efforts?

MR. HOLMAN: Objection. Relevance.

A I do not know what features Bruker emphasizes as part of sales.

Q And the same is true for the Xenium products, right?

MR. HOLMAN: Same objection. Relevance.

A Sir, my comment is the same.

Q Have you ever used Xenium or genomics?

A Sir, I've never used Xenium, but I'm familiar with Xenium, insofar as I describe it in my declaration, and its relationship to the '554 patent claims.

Q When was the first time you heard of Xenium?

A I probably heard of Xenium, sir, well before I got involved in this case.

Q Do you know for sure one way or the other?

A I certainly couldn't give you an exact

date as to when, but I've heard the -- I've heard the name Xenium around.

Q And when did you first become familiar with how Xenium worked?

A I think I probably became familiar with Xenium and how it worked in relationship to the '554 patent in this case, as I describe in this declaration, sir.

Q Okay. And have you ever used the Bruker genomics product?

A Sir, I've never used the Bruker genomics product.

Q When did you first hear of the Bruker genomics product?

A Sir, I hadn't heard of the Bruker genomics products, but I have heard of the Bruker NanoString CosMx product.

Q When did you first hear of the Bruker NanoString CosMX product?

A The Bruker NanoString CosMx product is something that I heard about in the context of this case, sir.

Q And the context of this case was when you first learned something about how it worked?

A Again, my understanding about the -- how it works, about the function of the CosMx Bruker NanoString, is in relationship to the claims of this patent, sir.

Q And you first came to that understanding in connection with your work on this case?

A That's correct, sir. My understanding of the Bruker NanoString CosMx case -- product, excuse me, relates to this case and the elements of the '554 patent.

Q When were you first contacted to assist with this case?

A I don't recall the exact date, but it would have been 2024, sir.

Q Did you review 10x's preliminary response in this case. Do you know what that is?

A I do not know what that is, sir. What I know, in relationship to response, that has to do with Dr. Czymmek's declaration and related

documents, as I described in this declaration.

Q Now, are you aware that prior to you being retained in this case, 10x had retained a different expert to work on this case?

A Sir, I have no knowledge of any of that.

Q So you didn't review the prior declaration submitted by another expert by 10x in this case?

A Sir, I have not reviewed said declaration.

Q Did you ever look at any customer surveys regarding what features of the Xenium or CosMx products are important to customers?

MR. HOLMAN: Objection. Relevance. Scope.

A Sir, the closest that I could come to that is what's described on paragraph 130 of my declaration. So there, I include -- I include some commentary by industry users that highlight the ability of these products to deliver, as described in paragraph 130.

Q Okay. So, with regard to the -- I think you only discuss Xenium in paragraph 130.

A It's true to say that all of the comments in paragraph 130 relate to praise for Xenium.

Q Now, what are the features of Xenium, as in your words, enable the Xenium product to, quote, deliver?

MR. HOLMAN: Objection. Form.

A Well, sir, these are not my words. But as I discuss on paragraph 130, Dr. Pi a talks about the innovative combination of hardware and software, including the bench workflow, the force analysis software. Dr. Luciano talks about streamlining the process from tissue handling to data interpretation. Dr. Peroni talks about the ability to provide high-resolution spatial data. Dr. Simon Gregory talks about the credible resolution.

Q Okay. Now, Dr. Pi a, you said, referred to the intuitive design of Xenium's bench workflow, right?

A Well, yeah. The exact sentence says the intuitive design of Xenium's bench workflow and post-run analysis software.

Q Okay.

A And the ability to provide greater depth and breadth that prior studies couldn't.

Q So let's take each of those bit by bit.

Do you know what Dr. Pi a is talking about when he or she refers to the intuitive design of the bench workflow?

A I think what Dr. Pi a is referring to is the fact that this is integrated monolithic assembly that is automated, that you can put in the sample and then out comes the analysis. That entire workflow.

Q Now, what about the post-run analysis software? Do you know what features the post-run analysis software provides in Xenium?

A Sir, I don't know exactly what features the post-run analysis software provide in Xenium.

I'd like to also, for the record, just mention that this discussion about industry praise

is relevant insofar as it provides evidence that the invention is not obvious. That's my understanding of why this praise is relevant insofar as it relates to objective indicia. And further support the idea that the '554 patent invention is not obvious.

Q Okay. Now, when it refers to bench workflow, what is the bench workflow for Xenium; do you know?

A Sir, as I've said, I'm not exactly sure what is meant by bench workflow here.

Q Okay. You're also not sure what's meant by post-run analysis software?

A I think we have to ask Dr. Pi a what's meant by post-run analysis software.

Q Okay. Do you know what steps are involved in preparing a sample for use on the Xenium instrument?

A Sir, I do not know exactly what steps are met for preparing a sample use of Xenium. I only know what combination of attributes of Xenium tie to the '554 patent, as I describe in the

proceeding pages of this declaration.

Q Do you know what level of resolution the Xenium instrument offers?

A Sir, in terms of the exact numbers of resolution, what the numbers are, I do not know what resolution Xenium offers.

Q Okay. Now, you wouldn't purport to know what features of CosMx that made CosMx commercially successful, right?

MR. HOLMAN: Objection. Form.

A Sir, I know what features of CosMx relate to the '554 patent, as I described, point by point, in this document.

Q I was asking something different. Do you know what features of CosMx made CosMx commercially successful?

MR. HOLMAN: Objection. Form.

A Sir, I wouldn't be able to speculate on what features made it commercially successfully.

Q Do you know what features made Xenium commercially successfully?

MR. HOLMAN: Objection. Form.

A Same answer, sir, I don't know what features exactly makes it commercially successful.

Q All right. Let's go to paragraph 112 of your declaration regarding obviousness.

Do you have paragraph 112?

A Yes, sir.

Q This is where you lay out your understanding of obviousness, correct?

A I wouldn't go that far, sir. It's not just in paragraph 112.

Q I'm sorry. I meant to say paragraph 12.

A Paragraph 12.

Q This section is where you lay out your understanding of the legal standards for obviousness, paragraphs 12 through 18, correct?

A Yes, sir. My understanding of obviousness is contained within these paragraphs.

Q All right. Now in paragraph 12 -- paragraph 13 --

A Say it again, sorry.

Q In paragraph 13, you state that

obviousness is ultimately a question of why.

Do you see that?

A Yes. That's what I say.

Q Okay. Do you have an understanding -- let me ask it this way: What is your understanding of what it means for something to be a question of why?

A Well, I mean, I would say it's exactly as I say in this paragraph. The scope and content of the prior art. The differences between the prior art and the claimed invention, level of ordinary skill in the art. The secondary considerations, including objective indicia.

But, I would also like to say that, you know, this discussion is further elaborated in the other -- in the additional paragraphs in this section.

Q Okay. How is a question of law different than a question of fact? Do you know?

A I'm not a lawyer. I don't know the difference in that terminology, sir.

Q So, do you know what you're referring

to here when you say a question of law?

A I understand that the -- my understanding is that the law refers to these points that I raise in this paragraph.

Q But you don't know the difference between a question of law or a question of fact?

A Sir, I've never heard the term "question of fact," so I don't know how -- I don't know how to interpret a question of fact. You're the lawyer. You would have to educate me on exactly what a question of law is and what a question of fact is.

Q So, you drafted this declaration, right? You understand what's in here, right?

A I do understand what is in my declaration, sir, yes.

Q Okay. So when you refer to a question of law, what are you referring to?

A What I'm referring to there is the idea that, ultimately, the law lays out what is and isn't obvious. The obviousness is -- the meaning of obviousness has a meaning in law. That's what

I mean.

Q Okay.

A In other words, the meaning -- the meaning of the term "obviousness" might mean something in patent law. It might mean something else in colloquial usage. But the -- but exactly as I lay out in this section on obviousness, is how I view I should interpret obviousness in the context of this declaration, in the context of this case, sir.

Q Now, do you know whether, in deciding whether the patent claim was obvious, that it's flexible or it's a strict inquiry; do you know?

MR. HOLMAN: Objection. Form.

A I think you'd have to define for me what you mean by "flexible" or "strict inquiry." This jargon, I don't know the meaning in this context, sir.

Q What's your misunderstanding? Is it your understanding that deciding whether something is obvious, you need to be strict about it or is it something that's flexible?

A Well, my understanding, sir, is exactly as I've written here. Paragraph 15 would be a good -- a good list of criteria that I believe are important in characterizing something as obvious or not vis- -vis patent claims.

Q Okay. So, on that note, regarding paragraph 15, is it your understanding that for a claim to be obvious, based on combining two distinct concepts in the prior art, there needs to be an expressed teaching in the art to combine those concepts?

A What I would say, sir, is exactly what I say here. There must be a reason why it would have been obvious to modify the prior art or to combine elements to arrive at the claimed invention.

Q Is it your understanding that there needs to be an expressed teaching of the art to combine those concepts; do you know?

A Sir, my understanding is what I say in the second paragraph. My understanding is that the patent challenger, you have the burden to show

that a POSA has a reason to combine the elements in the matter claimed by the certain obviousness. If you were just combining different references of the known art.

Q Do you have an understanding, one way or the other, whether to show obviousness by combining concepts that are in the art, there has to be an expressed teaching to combine those concepts?

Do you know one way or the other?

A I'm not sure what you mean by "one way or the other."

I think it's very clear what I mean, as I describe in this paragraph.

Q Okay. I'm asking the specifics. Say there's two concepts in the prior art, A and B. If someone is making an obviousness argument based on combining A and B, does there need to be an expressed teaching of the art to combine A and B for that person to be successful in making that argument?

MR. HOLMAN: Objection. Form.

A There must have been a reason why it would have been obvious to combine those elements to arrive at the claimed invention. Exactly as I said.

Q Now, does that reason need to include an expressed teaching to combine those concepts? Do you know?

MR. HOLMAN: Objection. Form.

A I'm not sure what you mean by "expressed teaching," sir.

Q Something that expressly says combine A and B.

A Sir, if an expressed teaching means that it would have been obvious, if there's a reason for why it would have been obvious, then I think it's -- then it would fall under the category of obviousness. But, again, there must have been a reason why one would have taken A and B and combined them.

Q Okay. I'm asking something different.

For there to be a reason sufficient to show obviousness, does that reason need to include

an expressed teaching in the art that says combine A and B? Do you know?

MR. HOLMAN: Objection. Form.

Q If you don't know, just let me know, but I'm just asking if you know one way or the other.

MR. HOLMAN: Objection. Form.

A Again, I'm not exactly sure what you're getting at, sir, here. I think it's clear what I mean when I say something is obvious in the context of the '554 patent, as I describe in these sections.

Q Let me try to ask it one more time.

Do you know, one way or the other, either yes or no, whether there needs to be an expressed teaching in the art to combine two concepts to show obviousness based on the combination of those two concepts?

MR. HOLMAN: Objection. Form.

A Again, there must have been a reason why you would combine A and B to arrive at the claimed invention.

Q And your understanding is that that reason needs to include an expressed teaching, correct?

MR. HOLMAN: Objection. Form.

A Sir, I'm not sure what you mean by "expressed teaching," again.

Q Okay. And you're not sure if the obviousness analysis is one that's flexible or strict, right? You just don't understand what I'm talking about when I raise that question?

MR. HOLMAN: Objection. Form.

A Again, I'll say it again, the -- my feelings about obviousness, as related to this case, are documented in this section of my declaration.

Q These are your feelings about it?

A I misspoke. Not my feelings. This is my understanding.

Q Okay. And I'm probing that understanding. I am going a little bit beyond that. I'm trying to see if you have an understanding beyond what's here.

My question is, do you have an understanding, one way or the other, whether the obviousness analysis is flexible or strict?

MR. HOLMAN: Objection. Form.

A I don't know exactly what you mean by flexible or strict, as I believe I've said before, sir.

Q Let me ask another question.

You talk about how there needs to be a reason why it would have been obvious to modify the prior art or to combine concepts that are in the art.

What are some of the rationale that might suffice to combine two consents in the prior art? Can you think of any?

A Sir, maybe what I can say about this is that it's Dr. Czymmek's assertion that one could get to the claims of the '554 patent simply by combining Chen, Shen, and Cai. That's Dr. Czymmek's assertion. But I rebut that assertion in this document. I don't think it is clear that there would have been a reason to

combine these elements in order to come up with the claimed system of the '554 patent.

So this would be an example, by Dr. Czymmek, of a case in which there are A, B, and C, Dr. Czymmek asserts that A, B, and C gets you to '554 patent.

But as I discuss in my declaration, I don't think there's any reason why one would have combined those.

Q Yeah, I was asking something different. I was just asking if you can think of any type of rationale that might justify combining two concepts in the prior art to render a claim obvious? What kind of rationale might work? Can you think of any?

MR. HOLMAN: Objection. Scope. Form.

A My answer is the same, sir. The example that I can give you would be the erroneous example of Dr. Czymmek, where he believes one can just combine A, B, and C to make the '554 patent. But I don't think that that's correct.

Q Do you know if common sense can be a

sufficient rationale to combine two concepts that are known to prior art?

A Sir, I don't know. Common sense seems like a very vague and nullified term to me. I'm not sure what you're getting at there.

Q Do you know if it can be a sufficient justification to prove something obvious as to argue that applying one concept to another concept would have been applying a known problem -- a known solution to a known problem? Would that kind of rationale justify defining obviousness? Do you know?

MR. HOLMAN: Objection. Form.

A Yeah, again, I'm not sure what you're getting at here, sir.

Q Do you know if something can be shown obvious by argument that the combination would be combining prior art elements, according to known methods to yield a predictable result?

MR. HOLMAN: Objection. Form.

A As I say in paragraph 15, sir, it's not -- you can't simply prove something obvious by

just combining -- but just demonstrating that each of these elements were known. There has to be a reason why you would modify the prior art to arrive at the claimed invention. Furthermore, there would have to be reasonable expectation of success, neither of which are met in this case.

Q I'm asking something different. Could it, in your view, be sufficient rationale to show obviousness to show that a POSA would have merely been combining prior art elements according to the known methods to get a predictable result?

Would that kind of rationale support obviousness?

MR. HOLMAN: Objection. Scope. Form.

A I'm not sure about that, sir, again.

Q Would -- could it potentially justify obviousness to show that a prior art combination of two things represents a simple substitution of one known element for another to obtain predictable results?

Would that work to show obviousness? Do you know?

MR. HOLMAN: Objection. Form. Scope.

A Sorry, I'm not sure.

Q Do you know if arguing that using a known technique to improve a similar device could be a sufficient rationale to show obviousness? Do you know?

MR. HOLMAN: Objection. Form.

A Again, all I know is what Dr. Czymmek stated about combining these elements and why I think that that is not correct.

Q Okay. I'm just asking you, could it ever be a sufficient rationale to justify obviousness to argue that applying a known technique to a known device is something that could justify obviousness? Do you know?

MR. HOLMAN: Objection. Form. Scope.

A My answer is the same, sir.

Q Which is what? You don't know?

A Just that I'm not sure what you're getting at and I'm not sure I understand the relevance of that to this discussion.

Q Okay. Could, you know, the argument

that it would be obvious to try a certain approach because there's a limited number of identified predictable solutions, possibly justified, defining of obviousness? Do you know?

MR. HOLMAN: Objection. Form. Scope.

A My answer is the same. I don't understand what you're getting at. It seems like you're discussing very general phenomenon that I'm not sure how it's relevant to this case.

Q Okay. How about if there was, you know, a teaching or a suggestion or a motivation in the prior art to combine two concepts? Would that justify the finding of obviousness? Could it?

MR. HOLMAN: Objection. Form.

A Again, there would have to be a good reason to combine these things to arrive to the claimed invention. And we would have to have a reasonable expectation that it would be successful in combining.

Q If there was an expressed teaching in the prior art to combine these two concepts, could

that be a good reason to justify obviousness? Do you know?

MR. HOLMAN: Objection. Form.

A Without understanding what you mean by "expressed teaching" and how it relates to this case, I can't really comment on that, sir.

Q Okay. Would it be a sufficient justification to show obviousness to argue that one is simply applying work in one field of endeavor that was known and applying either the same field or a different one based on design incentives or market forces?

Could that justify the finding of obviousness? Do you know?

MR. HOLMAN: Objection. Form. Scope.

A My answer is the same. I don't see how this relates to our discussion here.

Q Okay. Now let's take a look at paragraph 20 of your declaration.

A Yes, sir.

Q In paragraph 20, you talk quite a bit about how the Chen system was homebuilt.

Do you see that?

A Yes, I do.

Q Okay. Your understanding is that a prior art reference disclosing an instrument or apparatus that's homebuilt, that's something that weighs against relying upon that reference for obviousness, correct?

A Here, I'm simply pointing out that the instrumentation in Chen is homebuilt and it's also unwieldy and not space efficient. And, you know, by contrast, for example, to the integrated system described in the '554 patent.

Q Okay. So homebuilt, to you, weighs against obviousness in this case?

A Sir, I don't have any expressed opinions about homebuilt and obviousness. Nowhere in this do I say anything about that.

Q So you don't -- you wouldn't come in and say because the Chen reference is homebuilt, it's not a good reference for obviousness purposes? That's not your opinion, right?

MR. HOLMAN: Objection. Form.

A Sir, nowhere in this section do I use the language you just did about homebuilt and obviousness.

Q I'm just asking. And I'm not just asking about this section. Just generally, you don't contend that because the Chen reference is describing the system was homebuilt, it's a poor obviousness reference because of that fact? That's not your argument, right?

MR. HOLMAN: Objection. Form.

A Again, my answer is the same. That what I'm pointing out in paragraph 20 is that a POSA would have understood the system in Chen would have been unwieldy and not space efficient.

Q Okay. I want to be clear, you know, because the system in Chen was unwieldy and wasn't space efficient, you're not contending that that makes it a poor reference for obviousness purposes? That's not your argument, right?

A Sir, I don't have anything to say about obviousness with respect to -- explicitly with respect to homebuilt. But the relevance here is

that the system in Chen is far from the system of the '554 patent, which is an integrated system meant to work together in a monolithic way, as later demonstrated by the Xenium and CosMX systems.

Q Now, when you say "mono," what do you mean by that?

A An example of what I mean would have been the integrated system shown in Figure 2. Compact, integrated, seamlessly working together.

Q And your understanding is that the claims of the '554 patent are limited to what you describe as monolithic systems, correct?

MR. HOLMAN: Objection. Form.

A Sir, the claims of the '554 patent don't exclude the kind of apparatus shown in Figure 2. Regarding limitations, I don't have an opinion about that.

Q Your understanding is that the claims of the '554 patent exclude and don't encompass systems that are homebuilt, correct?

A Sir, I wouldn't say that claim 36

excludes homebuilt systems because nowhere in that -- nowhere in those claims do we have any language about that one way or the other. I'm merely pointing out that the integrated system described in claim 36 would be difficult to achieve with a homebuilt system. For the reason that a POSA would have understood that all these different elements of claim 36 would need to work together for the success.

Q Okay. Now claim 36, you believe, is limited to what you would describe as an integrated system, right?

A Sir, what I would say is that in order for the system described in claim 36 to be successful, all of these parts would have to work together as a cohesive goal. That would be my understanding.

Q And is that what you mean when you say "integrated"?

A By integrated, I mean the same as monolithic, the same as an example which would have been in Figure 2, as we just discussed.

Q Okay. So the claims, do you know, one way or the other, whether the claims of the '554 patent are limited to what you describe as integrated or monolithic systems?

MR. HOLMAN: Objection. Form.

A Sir, there's no -- I don't have an opinion about the limitations of these claims, but my understanding is that claim 36 were to include the kind of integrated system shown in this figure.

Q Is it limited, is claim 36 limited to systems that are integrated or monolithic? Do you have an opinion on that?

A Sir, I don't have an opinion on that.

Q Okay.

MR. HOLMAN: Are you about ready for a break soon?

MR. WALTER: Sure. If you guys want.

MS. KHANDURI: Let's take five minutes, ten minutes? How much?

THE WITNESS: Okay. Yeah, five minutes is good.

(Recess taken from 10:10 a.m. to 10:16 a.m.)

BY MR. WALTER:

Q Do you have any understanding, one way or the other, whether claim 36 of the '554 patent could encompass a system that's not integrated or monolithic? Do you know?

MR. HOLMAN: Objection. Form.

A Claim 36 doesn't explicitly have any language, one way or the other, about that. But it's my understanding that the -- in order for a successful commercial system, based on claim 36 to work, this would have to be in some integrated manner, would have to be integrated in order to adapt into a commercial product. That's the distinction in which I'm making about the homebuilt system, that it would have been difficult to adapt commercially, as I believe I say in paragraph 20.

Q And claim 36, there's no requirements that it be a commercial system, right?

A Correct.

Q Let's go to paragraph 60 of your declaration. Well, let me ask another question on this homebuilt and integrated monolithic stuff.

The reason you bring up the homebuilt and integrated monolithic is because, you know, your opinion is that if a homebuilt system is not integrated or monolithic, it wouldn't be a successful commercial product; is that right?

A That's one reason why I bring it up. One other point that I think is relevant to this discussion is that homebuilt systems, as of the kind described in Chen, are quite difficult to modify, even by POSAs. And, so, you know, Dr. Czymmek teaches that one could combine Chen, Shen, and Cai, though he's not exactly clear how one could combine them. One reason that I think the homebuilt nature is relevant is that it could be difficult to do that.

Q And, so, is it your view that commercial systems, those are easier to modify than homebuilt systems?

A My view on commercial systems is that

it could be easier to take a module of a commercial system and combine it with another module. In fact, that's frequently done in the field.

Q That depends on the commercial system, though, right?

A Of course. Depends on the commercial system.

Q Okay. And with regard to homebuilt systems, whether you can swap a module in or out, that depends on the homebuilt system, right?

A The -- the short answer is yes, it depends on the homebuilt system. But because of the sprawling nature of the homebuilt system, it's not as easy to swap in or out an element, as if you have a compact, integrated monolithic element that functions independently as one integrated system.

Q Is there any other reason you bring up this point about homebuilt and monolithic in an integrated system, beyond the two reasons you just mentioned?

A I will reiterate again. One is the sort of long-felt but unfelt -- unmet need to complete volumetric imaging system for determining three positional information, as I described in the objective indicia section of my declaration.

The other is, given my own personal experience of this and what I know about homebuilt systems, it's -- it can be quite difficult to modify one to add a feature of some other thing to the homebuilt device without wrecking the original purpose of the homebuilt device.

Q Now, with regard to that long-felt need, you're talking about that commercial product?

A Yes, specifically what I'm talking about is that the commercial product -- commercial product insofar as it relates to objective indicia. So it's my understanding that nonobviousness of an invention could relate to, for example, long-felt but unmet need for complete volumetric imaging system. And then I go, in my declaration, to describe the praise for such a

system.

Q And the long-felt need that you're talking about here was the long-felt need for the commercial product?

A More generally, the volumetric imaging system described by the '554 patent but instantiated the commercial products that I describe in my declaration, sir.

Q So the long-felt need wasn't for the commercial product, it was for the system?

MR. HOLMAN: Objection. Form.

A The response to the long-felt need is for the commercial systems. But the more general point is the complete system described by claim 36 in the '554 patent.

Q What fulfilled the long-felt need in this case?

A The need to, in a 3D sample, determine the 3D positional information of nucleic acid, sir.

Q And what, in your view, filled that need?

A One point that is not encompassed by MERFISH is the 3D nature of these products. In fact, you could determine the axial lateral nucleic acid.

Q What was the thing that filled that need?

A I don't know that I would say that there is a single thing that filled that need, but it certainly isn't the combination of multiplexing MERFISH with Cai and Chen.

Q Can you identify anything that filled that long-felt need that you identified?

A One feature would be determining the three-dimensional positional information of said one or more nucleic acid molecules. But, of course, you're asking me to give you a single example.

And I think it's important that we consider what's offered in claim 36 as a whole. So, you're asking me for individual things. Any one of these things in isolation is not sufficient to satisfy the entire claim 36, which should be

read as a whole.

Q Well, let me stick a little deeper on that. Are there any particular steps, individual steps in any of the claims that you contend are not a learned inventive?

MR. HOLMAN: Objection. Form.

A I don't have an opinion, strong opinion about what you're asking me, sir.

Q Okay. Is there any particular step in any of the claims of the '554 patent that you contend is not in the prior art?

A All I can say is that the prior art described by Dr. Czymmek, namely MERFISH combined with Chen and Cai, does not meet the specifications in claim 36.

Q Okay. If there's any particular step in many of the claims of the '554 patent that you contend is not in the prior art, please identify that now.

MR. HOLMAN: Objection. Form.

A I'd have to do a thorough analysis on that, sir. I couldn't give you an immediate

answer there.

Q What, if anything, is there that you contend is novel or inventive in any of the claims of the '554 patent?

MR. HOLMAN: Objection. Scope. Form.

A Sir, it's not really what I think is important or inventive, it's really about Dr. Czymmek's erroneous assertion that one can combine these prior art in order to come up with what is described in claim 36.

Q Okay. Sitting here today, as 10x's expert on obviousness, if there is anything that you contend is novel or inventive in any of the claims of the '554 patent, please identify that now.

MR. HOLMAN: Objection. Form. Scope.

A A number of assumptions in your statement there, sir. I wouldn't describe myself as 10x's expert on obviousness. Again, as I just said, you know, my role in this is refuting or rebutting Dr. Czymmek's erroneous assertion that one could achieve what is disclosed in the

'554 patent by combining Chen's MERFISH with Shen and Cai.

Q Sitting here today, as expert -- as 10x's expert on obviousness, do you have any opinion about whether there's anything novel or inventive in any of the claims of the '554 patent?

MR. HOLMAN: Objection. Form. Scope.

A Sir, my opinion has to do with Dr. Czymmek's opinion and why I think that is erroneous, as I describe in my declaration.

Q You know, sitting here today, as 10x's expert on obviousness, can you identify anything that you would contend is novel or inventive in any of the claims of the '554 patent?

MR. HOLMAN: Objection. Form. Scope.

A My answer is the same, sir. I wouldn't describe myself as 10x's expert on obviousness. My role in this is to refute the erroneous assertion of Dr. Czymmek, that one could arrive at claim 36 by combining MERFISH with Shen and Cai.

Q All right. Let's go to paragraph 60 of your declaration.

A Yes, sir.

Q Paragraph 60 is where you start to set forth your understanding of the legal standard for claim construction.

Right?

A Paragraph 60 is a preamble to an important discussion on temperature control and the meaning of that term vis- -vis the '554 patent, sir.

Q Okay. Now, I guess paragraph 60, this is where you set forth your understanding of the rules that apply when construing claims, right?

A Sir, paragraph 60 discloses exactly what I described in paragraph 60, that patent claims are given their ordinary meaning, as understood by a POSA at the time of November 3rd, 2015, in view of the patent specification and history. And that, also, my understanding that when a patent explicitly defines the claim term, the patent's definition is what matters in the context of this document.

Q All right. Now, beyond what's set

forth in paragraph 60, do you have any further understanding of the legal rules that apply when interpreting claims of the patent?

MR. HOLMAN: Objection. Form. Foundation.

A That's a very general question, sir, and I'm not a lawyer. I can't claim to have perfect knowledge of all legal terms in patent law.

Q Let me ask a few questions on this. We talked earlier about the prosecution history of the patent. Do you know what the specification of the patent is?

A My understanding is that the patent specification is the body of the patent, sir.

Q Do you know what's more important for interpreting claims, is it the specification or is it the prosecution history? Do you know?

MR. HOLMAN: Objection. Form.

A Sir, I'm not a lawyer. I don't know which is more important.

Q Do you know if the claim language is

more important than the specification and prosecution when it comes to interpreting claims? Do you know?

MR. HOLMAN: Objection. Form.

A Sir, I'm not a lawyer. I don't know which of these things you're saying is more important in the patent.

Q At the bottom of paragraph 60, as you pointed out, you state that when a patentee explicitly defines a claim term in the specification, definition controls.

Do you see that?

A I do.

Q Are there any other principles related to claim construction that you were informed of in drafting your report?

A Nothing comes to mind right now, sir. But, again, I'm not a lawyer. I'm not sure what principles you're referring to.

Q Now, do you rely on any explicit definitions in the patent for your opinions related to claim construction in this case?

A Sir, what I understand about definitions relate to temperature control in claim 36 and the meaning of that term.

Q Okay. Now, you state here that when a patentee explicitly defines a claim term in the specification the patent's definition controls.

Do you see that?

A I do.

Q Is there an explicit definition of the claim term "temperature control apparatus" in the '554 patent?

A Sir, if you're asking, like, does the patent explicitly define temperature control means X, I don't recall seeing that in the '554 patent.

But, as I say in paragraph 61, a POSA would have understood what the term temperature control meant, in light of the language from the specification of the patent and the dependent claims. And I give specific examples of exactly what I mean in paragraphs 62 and 63 of my declaration.

Q All right. But you don't contend

there's an explicit definition, right?

A As I said in paragraph 61, in my opinion, a POSA would have understood what that meant. And as I say in the first sentence of 62, a POSA would have also understood what temperature control meant in light of the language, as I spell out here.

Q Please identify for me where, in the '554 patent, you contend the patent provides an explicit definition of the term temperature control apparatus?

A Sir, I don't contend that the patent, as I just said, explicitly defines temperature control. My contention is that a POSA would have understood the meaning of temperature control in light of the language of the patent specification and the claims. And I give -- I give examples and I'm happy to read in paragraph 62.

Q Are you aware -- you're aware that in construing claims, it's appropriate to limit the claims to examples and embodiments in the specification, correct?

MR. HOLMAN: Objection. Form.

A Sir, you're the lawyer. I'm not sure what you're referring to there.

Q Okay. Do you know, one way or the other, whether it's appropriate to construe claims to be limited to examples and embodiments in the specification?

MR. HOLMAN: Objection. Form. Scope.

A My knowledge of the terms in the patent, and specifically with respect to temperature control, which is relevant in this discussion, because the sense in which temperature control in defined in the '554 patent is very different than what Dr. Czymmek asserts. In that sense, I have opinions about temperature control, as I spell out in paragraphs 62 and 63 of this declaration, sir.

Q Okay. I was asking something a little more general.

Do you know, one way or the other, whether there are any rules related to whether it's appropriate to limit claims in a patent to

examples or embodiments in the spec?

Do you know?

MR. HOLMAN: Objection. Form. Scope.

A Again, sir, my answer has to be the same. I'm not a lawyer, so I'm not sure exactly what you're referring to here.

Q Okay. And that's fine.

Let's say that in a patent, there's only a single embodiment. Do you know, one way or the other, whether, in those circumstances, it would be appropriate to construe the claims as being limited to only that embodiment?

MR. HOLMAN: Objection. Form.

A Sorry, sir, I don't have the knowledge to answer your question there.

Q Have you ever heard of the concept of a patentee disavowing or disclaiming claim scope?

MR. HOLMAN: Objection. Relevance. Scope.

A Sir, I have no idea what you're talking about.

Q You don't contend, in your report, that

there's any disavowed or disclaimer of claim scope in either the specification or the prosecution history, correct?

MR. HOLMAN: Objection. Form.

A My answer's the same. I really don't know what you're referring to.

Q Are you familiar with oil immersion lenses?

A Yes, I am, sir.

Q Is it accurate that in those lenses, an oil droplet is placed in the front of the lens and it's moved to contact the cover slip for the sample?

A Yeah. That is accurate, sir.

Q Now, have you ever heard the term thermal control system?

A Thermal control system? Yeah, I'm sure that I have heard that term.

Q Do you know what a thermal control system is in the context of the '554 patent?

A Well, I know what a temperature control system is and temperature control. If what you're

saying is equivalent to that term, then I do have strong opinions about what temperature control means in the context of the '554 patent.

Q I'm asking something different. Do you know what the term, I know we've been talking about temperature control apparatus. Do you have any understanding of what the -- what a thermal control system is, in the context of the '554 patent?

A I certainly understand what a temperature control system is.

Q A temperature control system or a temperature control apparatus?

A Certainly, temperature control apparatus, sir, as I described in paragraph 64 of my declaration.

Q Now, is the temperature control system the same thing as a temperature control apparatus?

A If we agree that system and apparatus are the same word, then it must be, right?

Q Well, I'm asking you, as the expert who's reviewed the patent.

Do you have an understanding of whether temperature control apparatus and temperature control system are the same in the context of the '554 patent?

A I mean, the particular terminology that I think is relevant here is temperature control apparatus, as described in claim 36.

Q Do you have an opinion as to whether a temperature control system is different from a temperature control apparatus?

A If we're talking about the meaning of those terms in the colloquial sense, I would use either one to describe the same thing.

Q Okay.

A But, again, the -- my opinions on temperature control apparatus, I'm using that phrase specifically because claim 36 refers to that term, temperature control apparatus.

Q Got it.

Now, if I were to introduce the term "thermal control system," would that, in your understanding, in the colloquial sense, mean the

same thing as temperature control apparatus?

A In colloquial usage, I would use that term apparatus, yes.

Q Take a look at claim 44 in the '554 patent.

A Yes, okay.

Q Do you see that? That refers to a thermal control system.

Do you have any understanding what's being referred to there?

A The way that I read that is a -- is, generally, a temperature control apparatus, sir.

Q Okay. Are you familiar with the principle that dependent claims need to be narrower than independent claims? Are you aware of that?

A I'm generally aware of that principle, yes, sir.

Q And in your view, thermal control system in claim 44 is the same thing as temperature control apparatus?

A In my view, those two terms are very

similar. I admit that I'm not exactly sure what the difference is in the context of claims 43 and 44, except to say that, of course, claim 43 specifies temperature control apparatus comprises a heat sink or Peltier element, sir.

Q Now, a heat sink and a Peltier, those are active cooling systems, correct?

A The Peltier element is an active cooling and heating system in the sense that one has to put energy into the system. Heat sink could be passive or it could be active, depending on the context.

Q Now, are you aware of any other kind of active cooling systems that a POSA would understand would be used, for example, with microscopy besides a heat sink or Peltier element?

MR. HOLMAN: Objection. Form.

A Well, in the context of the '554 patent, sir, as I describe in paragraph 62 of my declaration, there is terminology, heat sink in conjunction with a fan. So in that sense, in addition to Peltier elements and heat sinks, that

would be an example of something else.

Q But the fan would also be comparable to the heat sink in the '554 patent?

A I would say the reverse way, that heat sink appears in conjunction with a fan. In this case, heat sink occurs in conjunction with a Peltier cooler element later. So it's -- sir, I would have to review, in detail, the '554 patent to make the claim that fan always appears with heat.

Q Now, the heat sink and Peltier element, those are parts of claim 43, correct?

A 43 does describe temperature control apparatus comprising heat sink or a Peltier element.

Q And you understand that Bruker and Dr. Czymmek presented arguments that claim 43's use of the heat sink or Peltier element would be obvious, correct?

A What I understand, sir, is that there's a distinction between temperature control in the '554 patent and what Dr. Czymmek asserts in his

declaration. Temperature control in the context of the '554 patent refers to heating and cooling. Dr. Czymmek's declaration discusses heating, temperature control in the context of, at best, heating and maintaining heat. That's the distinction that I make in my declaration.

Q Okay. Now, Dr. Czymmek, he actually has opinions on whether a heat sink or a Peltier element would be obvious, correct?

A I think in order to assess your assertion there, I'd have to see Dr. Czymmek's declaration. You'd have to point me to exactly what you're talking about.

Q Okay. You don't remember?

A It's just that I'd like to see the document to be sure we're talking about the same thing.

Q I'll give you Exhibit 1002. Dr. Czymmek's declaration.

(NanoString Exhibit 1002 previously marked for identification and retained by counsel.)

Q Go to page 114. If you take a look at paragraph 233, you can see Dr. Czymmek's opinions about how heat sinks and Peltier elements were well-known and used to achieve temperature control.

Do you see that?

A I do see paragraph 223 and Dr. Czymmek's assertion there, sir, yes.

Q Okay. And you did not respond to Dr. Czymmek's opinions on paragraph 43, correct?

A Paragraph 43?

Q Excuse me, claim 43. You did not -- let me ask the question again so it's clear. You did not respond to Dr. Czymmek's opinions regarding claim 43, correct?

MR. HOLMAN: Objection. Form.

A I think I do respond because, in my declaration, for example, in paragraph 69, I explain, at length, the difference between temperature control apparatus and the meaning of the '554 patent versus what Dr. Czymmek is asserting in his declaration.

Q Okay. Well, Dr. Czymmek says heat sink or Peltier element would be obvious. He says that, right?

A Actually, what Dr. Czymmek says is that a POSA would have understood that heat sinks and Peltier elements were well-known.

Q Well, take a look at the last sentence. He says, paragraph 233, it's my further opinion that it would have been obvious to a POSA to include heat sinks or Peltier elements as part of the temperature control apparatus for the benefit of improved temperature control and cooling capabilities.

Do you see that?

A I do see that, yes.

Q If there is any place in your declaration where you believe you respond to Dr. Czymmek's opinions on claim 43, please, identify where that is now.

A I'm not arguing that Dr. Czymmek -- I'm not arguing with Dr. Czymmek that a POSA would have known that heat sinks and Peltier elements

could be used to control temperature. Rather, what I'm saying is that the specification of the '554 patent, including claim 43, with respect to, additionally, the independent claim 36, is not the same as what is described in Chen, Cai, and Shen, as Dr. Czymmek asserts.

Q Is there any place in your declaration where you respond to Dr. Czymmek's opinions regarding claim 43?

A Again, my opinions on this matter are described in paragraphs 69, 70, and 71. That there's an important distinction between the temperature control, as defined by the '554 patent, versus the temperature control included in the Cai, Shen, and Chen.

Q Any place else, other than those paragraphs you just identified, where you respond to Dr. Czymmek's opinions on claim 34?

A Yes. There is additional information in paragraph 60 through 64, for example. Where, again, I discuss what is meant by temperature control apparatus in the context of the

'554 patent. And the distinction between what is done in Chen, Shen, and Cai.

Q Any place else?

A Let's see, we discussed 72, 73, 74, 75. These are additional relevant paragraphs vis- -vis temperature control in the '554 patent and my disagreements with Dr. Czymmek's opinion of this matter.

Q Now, if you go to paragraph 233 of Dr. Czymmek's opinion.

A Yes.

Q Do you disagree with Dr. Czymmek when he says "It is my opinion it would have been obvious to include heat sinks or Peltier elements as part of the temperature control apparatus for the benefit of improved temperature control, including capabilities"?

Do you disagree with Dr. Czymmek about that?

A Again, I'm not disputing that it would have been known that heat sinks or Peltier elements can be used to cool and heat. But

rather, the relevant part, I think, here is what exactly we mean in the '554 patents, which is distinct from the combination of Chen, Cai, and Shen. In particular, claim 43 is using temperature control to mean heating and cooling vis- -vis the independent claim 36. And that is different than what Dr. Czymmek outlines, as I explain in my declaration.

Q So you don't dispute what Dr. Czymmek says in the last paragraph, last sentence of paragraph 233 of his declaration, correct?

A Again, what I would agree with is that a POSA would have known that heat sinks and Peltier elements exist. But that's different than the use of them in claim 43 in support of claim 36, the entire claim, as an integrated system in the '554 patent. My understanding is that we have to view all of the dependent claims in the context of the independent claim. And in that sense, the meaning of temperature control in 43 is different than what Dr. Czymmek asserts is contained within Chen, Shen, and Cai.

Q Okay. Is there any place where you present opinions that a person of ordinary skill in the art wouldn't have found it obvious to use heat sink or Peltier elements with Chen, Cai, or Shen?

MR. HOLMAN: Objection. Form.

A Again, a POSA would have understood what a heat sink and Peltier element is. The distinction that I'm drawing in my declaration is the meaning of temperature control in view of these terms, heat sink and Peltier element, for the claims of the '554 patent, which is distinct from what Dr. Czymmek describes temperature control means in the context of Shen, Cai, and Chen.

Q That's not really answering my question.

I'll try one more time.

Is there any place where you present opinions that a person of ordinary skill in the art wouldn't have found it obvious to use a heat sink or Peltier element with Chen, Cai, or Shen?

MR. HOLMAN: Objection. Form.

A Again, a person of skill in the art would know what heat sinks and Peltier elements are, in the context of temperature controls, but the point that I'm making in my declaration is that the meaning of temperature control vis- -vis these element, in the context of the '554 patent, is distinct from what Dr. Czymmek is asserting how temperature control is used in Chen, Shen, and Cai.

Q Okay. Now, would a person of ordinary skill in the art have understood that the use of heat sink or Peltier element would provide a benefit of improved temperature control and cooling capabilities? Would a person of skill have understood that in 2015?

MR. HOLMAN: Objection. Form.

A I mean, I think it depends on what we mean exactly by improved temperature control and cooling capabilities. Improved relative to what, for example?

Q Relative to a system that didn't have a

heat sink or Peltier element.

A I mean --

MR. HOLMAN: Objection. Form.

A -- if you're asking do heat sinks and Peltier elements provide temperature control, I would have to agree. But the context of this matter, insofar as we're discussing the '554 patent and its distinction from what Dr. Czymmek asserts, is prior art in Shen, Cai, and Chen.

Q Why, in 2015, would a person of skill in the art have used heat sink or a Peltier element?

A A person skilled in the art would have known, in 2015, that a heat sink or Peltier element could be an element of temperature control.

Q And why would a person of skill in the art have been motivated, in 2015, to utilize those elements of temperature control, namely, a heat sink or Peltier element?

MR. HOLMAN: Objection. Form.

A I think you're asking a very general question. And my answer has to be, also, very general. It depends on what the goals of this person were. Again, the point that is relevant here is the context of heat sink, Peltier element, temperature control, as far as the meaning of temperature control, in the '554 patent, claim 43, which is heating and cooling, as I've described in my declaration, in the context of the entire '554 patent.

Furthermore, this context of heating and cooling is relevant only insofar as we consider the entire claim 36.

Q Okay. Let's -- you keep bringing up heating and cooling. So just one topic on that. So let's go to that.

You agree that a heat sink and a Peltier element, those are active cooling elements, right?

A Heat sink is an active cooling element insofar as the language of the '554 patent. Peltier elements would be considered to be active

heating and cooling elements in the sense that you put in energy and then the element can either heat or cool.

Q Okay. You understand that a heat sink or Peltier element, those are elements that would be used for cooling parts of the system, right?

A Sir, a Peltier element could also be using used for heating part of the system.

Q Let's take a look at your paragraph 62. You can tell me if you want to change your testimony. "Dependent claim 43 recites a system in which the temperature control apparatus 'comprises a heat sink or a Peltier element,' elements that a POSA would have recognized as being used for cooling parts of a system."

Do you see that?

A Sir, I do see that.

Q Okay. You don't want to change that, right?

A Sir, nothing that I say there precludes the use of a Peltier element as a heating element. I'm merely pointing out that dependent claim 43

recites a system in which the heat sink or Peltier element could have been used for cooling parts of the system. So, no, I don't feel I need to change my testimony.

Q Okay. A person of skill in the art would have recognized that the heat sink or Peltier element in claim 43 would have been recognized as being used for cooling parts of the system, correct?

A They would have recognized that, yes.

Q And that, in your view, the use of a heat sink or Peltier element satisfies the cooling aspect of your construction of temperature control apparatus, right?

A It satisfies cooling. But, again, as I just said, a Peltier element could be used for heating, and a heat sink could be used to remove heat generated as part of the Peltier element's heating operation. This is also something that a POSA would have known in the art.

Q And Dr. Czymmek contends that the heat sink and Peltier elements would have been obvious,

right?

MR. HOLMAN: Objection. Form.

A Dr. Czymmek, my understanding of Dr. Czymmek's sentence there is that a POSA would have known that heat sinks or Peltier elements could be part of the temperature control apparatus. But, again, you know, the particular points that we're discussing here is heating and cooling in the context of the '554 patent as claim 43 and its relationship to independent claim in 36, which is distinct from the meaning of temperature control in Chen, Cai, and Shen.

Q Okay. Tell me again where you present the rebuttal on to Dr. Czymmek's opinion that it would have been obvious to use a heat sink or a Peltier for the benefit of improved temperature control and cooling and heating capabilities. Tell me again where that is in your declaration.

A Sir, I never asserted that heat sinks or Peltier elements wouldn't have been known to a POSA, that it isn't obvious what a heat sink or Peltier element does. Rather, as I've said

before, the material in my declaration, including the paragraphs that I previously stated and the stenographer has on record, have to do with the particular language and meaning of temperature control apparatus in the context of the '554 patent's claim 43 and independent claim 36. Which is distinct from the meaning of temperature control in Czymmek, as referenced in Cai, Chen, and Shen.

Q If there is any place in your declaration where you provide a rebuttal to Dr. Czymmek's opinions that it would have been obvious to use a heat sink or Peltier element for the benefit of improved temperature control and cooling capabilities, tell me where those paragraphs are.

MR. HOLMAN: Objection. Form.

A I don't have anything further to say about this than what I said before, sir.

Q Just tell me, again, what paragraph -- if there's a paragraph that you think best encapsulate your opinion of that, tell me what

your best paragraph is.

MR. HOLMAN: Objection. Form.

A Again, I'm not disputing the fact that a POSA would have known what a heat sink or a Peltier element is. Rather, the paragraphs that I've said before have to do with the meaning of temperature control in the context of the '554 patent's claim 43 and independent claim 36, sir.

MR. WALTER: Let's go on record and say I think that's nonresponsive.

Q Now, if you had a system that maintains a sample of a particular temperature, would that be sufficient to meet the temperature control apparatus element of claim 1?

MR. HOLMAN: Objection. Form. Foundation.

A You know, I don't have a strong opinion on this, sir. I'd have to review exactly what claim 1 says or doesn't say about temperature control.

My opinions in my declaration, as are

stated in the declaration, specifically refer to claim 43 and its relationship to claim 36.

So I'd have to say that I don't have an opinion about this or at least I would need a lot more time to form an educated opinion about maintaining temperature in the context of claim 1.

Q Is increasing the temperature of a sample so that you make it a particular temperature, is that a form of temperature control?

A It's a form of temperature control, but not temperature control as defined in the '554 patent, as I describe in paragraph 62 of my declaration.

Q Now, you just said it was defined in the '554 patent. Tell me where the definition of temperature control is defined in the '554 patent.

Where's that explicit definition?

A Yes, as I said previously, a POSA would have understood temperature control from the local context of all of the language of the patent, as I describe in 62.

So, I can't point you to an exact place. But as I say in paragraph 62, there are numerous examples of temperature control in the sense of heating and cooling, as I outline in that paragraph.

Q Is there a definition? You just said there was a definition. I just want to know if there's a definition?

A I'm using definition to mean -- in the sense of how we should interpret the meaning of temperature control, sir. There is no single sentence that I can point you to. However, contextually, a POSA would have understood heating and cooling from the numerous examples that I illustrate in paragraphs 62 and 63.

Q But you agree that increasing the temperature of a sample so that you can make it a particular temperature, you agree that's a form of temperature control, right?

MR. HOLMAN: Objection. Form.

A Not in the sense of '554 patent, sir, as I've described and as it relates to claim 43

and claim 36. Not in that sense.

Q Okay. Is cooling a sample so that you bring it down to a particular temperature, is that a form of temperature control?

A Cooling is also a form of temperature control. But the language in the '554 patent is inclusive of heating and cooling, as I describe in my declaration.

Q Not just inclusive. You believe that it requires heating and cooling, right? That's your opinion?

A What I would assert, and I have asserted in my declaration, is that a POSA would have interpreted the language "temperature control" to meaning heating and cooling because of the numerous examples of heating and cooling in the '554 patent. What's relevant here is what a POSA would determine from reading the '554 patent, as I spell out in paragraph 62 and 63.

Q And you base that on the examples in the '554 patent?

MR. HOLMAN: Objection. Form.

A I base that on exactly what I say in paragraph 62 and 63, which are numerous examples of heating and cooling.

Q Okay. And your understanding is that the rules of claim construction are that claims should be limited based on the examples in the specification, correct?

MR. HOLMAN: Objection. Scope. Form.

A What I understand about claim construction is contained within paragraph 62. Beyond that, I'm not a lawyer. I wouldn't attribute that additional knowledge to me.

Q Okay. Now, is it possible to have a system that maintains the temperature of a sample at a particular temperature without active cooling?

A Yes. It's possible to maintain a temperature without active cooling by turning off the heating.

Q Okay. Is it possible to have a system that maintains the temperature of a sample at a particular temperature without active heat?

A Only room temperature.

Q What about if you're in a cold environment?

A I mean, if an environment is -- if the bath, the surrounding environment, is a certain temperature, if you wait enough time, everything will become that temperature. Of course in practice, when one wants to heat and cool, then one would use a temperature apparatus that provides both of those capabilities. In any real experiment, one doesn't want to wait around forever until you reach the thermal equilibrium of a bath.

Q What about a refrigerator? Can that be used as a temperature control system?

A A refrigerator would be an example of active cooling, where one puts energy in to actively cool.

Q Now, could a refrigerator be considered a temperature control system?

MR. HOLMAN: Objection. Form.

A Not in the sense of the '554 patent,

sir. Because the refrigerator, as it's conventionally known, holds temperature at a particular temperature, namely a cold temperature.

Q Okay. So a refrigerator is a system that maintains a temperature, a particular temperature that's cold, but you would not call it a temperature control apparatus in the context of the '554 patent because it doesn't include an active heating component; is that right?

MR. HOLMAN: Objection. Form.

A Again, the '554 patent, the meaning of temperature control is one which encompasses heating and cooling. The example you just gave of a refrigerator merely maintains temperature.

Q So, a refrigerator is not a temperature control apparatus in the context of the '554 patent, right?

A The -- again, the claim 43 explicitly refers to comprising a heat sink or a Peltier element. You know, in that sense, of course a refrigerator is not a heat sink or Peltier element.

So, trivially, a refrigerator is not the same thing as claimed in claim 43, vis- -vis global context of claim 36.

Q And also not a temperature control apparatus within the context of claim 36, too, right?

MR. HOLMAN: Objection. Form.

A I guess I'll just repeat exactly what I said, which is that claim 43 specifies the system of claim 36 wherein said temperature control apparatus comprises a heat sink or Peltier element.

Q Well, that actually wasn't an answer at all.

I'm just asking about the term "temperature control apparatus," within the context of claim 36.

Is a refrigerator a temperature control apparatus, as that term is used within claim 36?

A Well, I'll refer kind of verbatim to the declaration here. In my opinion, a POSA would have understood the phrase temperature control in

claim 36, in view of the specification to mean the ability to actively heat and actively cool an apparatus.

So, the question is, does a refrigerator actively heat and actively cool an apparatus? Certainly, in the sense in which you mean it, I think the answer is no. As you said yourself, a refrigerator maintains a constant cool temperature. Ergo by exactly what I say in paragraph 61, a refrigerator would not reach that definition.

Q And that's because although it maintains a constant cool temperature, it doesn't have active heating; is that right?

A Again, as I say in my declaration, in my opinion, a POSA would have understood the phrase temperature control in claim 36, in view of this specification, to mean the ability to actively heat and actively cool an apparatus.

Q I just want to be clear. Your understanding is a refrigerator doesn't have the active heat; is that right?

MR. HOLMAN: Objection. Form.

A Refrigerator, I mean, you know, I could conceive of a refrigerator that might have the ability to actively heat and actively cool an apparatus. But as far as what is meant in the '554 patent is exactly the language that I just said. It means the ability to actively heat and actively cool an apparatus. A refrigerator in our homes does not have that capability as a matter of routine.

Q And so, the refrigerator will maintain things at a constant temperature but it is not a temperature control apparatus, as used in the claims; is that right?

MR. HOLMAN: Objection. Form. Relevance.

A Sir, I'll repeat what I said. That in my opinion, a POSA would have understood the phrase temperature control, in the '554 patent, to mean the ability to actively heat and actively cool an apparatus. If a refrigerator, what you're calling a refrigerator, could do that, then it

would fall within that specification. But I think the sense in what you mean, refrigerator does not meet that bar.

Q But you agree that refrigerator maintains things at a constant cool temperature; is that right?

MR. HOLMAN: Objection to form.

A I think, you know, if we're talking about the refrigerator in the common use of the term, a refrigerator is understood to maintain a constant temperature in your home.

Q If you had a system that maintained a temperature at a particular level and did it with only active heating, but didn't have active cooling, would that be a system that provided temperature control?

A Not in the sense in which I've defined it in my declaration and which the '554 patent defines it.

Q How about a system that checks to see if the sample is below a desired temperature, and if it is, it heats it up to that temperature and

it stops when it reaches that temperature? And then if it starts to drop a bit, a passive cooling requires a bit more to maintain the desired temperature?

Would that be temperature controlled?

MR. HOLMAN: Objection. Form. Foundation.

A I think the problem is that you're invoking the term "passive cooling," sir, which doesn't fall within the rubric of the '554 patent.

Q So that system would not be temperature control, that I just described?

MR. HOLMAN: Objection. Form.

A I'm not sure exactly what you're referring to there. But one thing that I can tell you is not temperature control, in the same sense in which we've been dancing around this topic, is the objective heater disclosed in Chen.

This would be an example of a system that heats to 37 degrees. There's no mention of any cooling capacity; therefore, it doesn't rise to the bar mentioned in my declaration of the

'554 patent.

Q Well, can we take another stab at it? I'm trying to describe a system that measures the temperature of your sample. And if it's below the desired temperature, heats it up to that temperature and then it stops when it reaches that temperature, and then if it starts to drop a bit. From passive cooling, it requires a bit more heat to maintain the desired temperature.

Would that be a form of temperature control?

MR. HOLMAN: Objection. Form.

A Not in the '554 patent because you have not explicitly given me active cooling.

Q Okay. I need to give you another simple example.

How about my house in San Francisco, if I'm lucky and get really good weather?

A I have no idea what the characteristics of your house in San Francisco are.

Q I'm going to give a little more information.

Now, you know, we're lucky, we don't even to have air-conditioning in our home. I have a heater in my house that heats our house up to 72. Cools a little bit, it falls below 72, it gives a bit more heat. But we never have -- we don't have an air conditioner on our home.

Would that be a temperature control system?

MR. HOLMAN: Objection. Form. Foundation. Relevance.

A From what you're describing, sir, it sounds a lot like the objective heater in Chen, which I describe, in paragraph 72 of my declaration, doesn't meet the definition of a '554 patent.

Q Okay. Very good.

Have you ever heard of the term "optical channel," in connection with microscopy?

A Optical channel in connection with microscopy? Not that I can recall. You'd have to give me a bit more context as to what you mean by optical channel.

Q Okay. You've never heard that term used before?

A I mean, I hesitate to say never, but it doesn't ring a bell in my memory. I mean, yeah, I think you'd have to be a little more specific about -- are you talking about a fluorescence imaging channel? In that case, you know, I know what's on the emission side. Are you talking about an excitation channel? Optical channel is a little vague for me to know what you're talking about, sir.

MR. HOLMAN: Can we take a break soon? It's been about an hour.

MR. WALTER: Yeah, pretty soon.

Q Have you ever heard of the term "channel" used in the context of a microscopic -- a system for microscopy?

A I would say that I've heard of multichannel fluorescence, referring to more than one emission or excitation channel.

Q Okay. I think we're on the same page.

A Okay.

Q Now in that context, when you have multiple channels, you need to have a separate light source for each channel, right?

A Well, not necessarily. Some fluorophores have different emission channels but are serviced by the same light source.

Q You can have multiple channels with only a single light source?

A Oh, yeah.

Q How might that work?

A Well, you could have an emission channel that detects GFP fluorescence, but GFP could be excited by multiple wavelengths of light. Alternatively, you could have one channel of excitation that excites GFP that could detect to emission in two separate emission channels.

Q Is it possible to have a single light source that's, like, the broadband light source, where you apply filters to filter out only certain wavelength ranges?

MR. HOLMAN: Objection. Scope. Form.

A It is possible to have such a light

source in fluorescence emitting systems.

Q And how do those work?

A It's a very general question. I'm not sure what you're getting at. But you'll have a light source and then you put different filters in front of it, just as you said, sir.

Q And what kind of broadband light sources are there that are available that might be used in that type of setup?

MR. HOLMAN: Objection. Scope.

A You could have arc lamp, you could have LEDs, those would be two examples of light sources.

Q Any others?

A You could have a white light laser for example.

Q Any others?

A There may be others, but these are the ones that come readily into my mind.

Q And how long have those kinds of light sources been available for? Were they known to people of skill in the art in 2015?

A All of those light sources were around in 2015, sir.

Q How about the filters that you talked about?

A Well, I mean, filters are being created all the time. So there could be some filters that were around and some filters that have been built subsequent to 2015.

MR. WALTER: All right. We can go ahead and take a break now.

(Recess taken from 11:18 a.m. to 11:31 a.m.)

BY MR. WALTER:

Q All right. Let's go to paragraph 11 of your declaration, Dr. Shroff.

And in paragraph 11, you express opinions on the level of ordinary skill in the art, correct?

A Uh-huh. Yes, I do.

Q And you reviewed Dr. Czymmek's opinions on that, correct?

A Yes.

Q And in your report, do you identify any points of disagreements with Dr. Czymmek regarding his definition of the level of person of ordinary skill in the art?

A Just to make sure I understand your question.

Are you asking do I disagree with Dr. Czymmek's definition of a POSA?

Q Well, I'm asking something else first. I'm asking, first, if there's anywhere in your declaration, Exhibit 2024, where you identify any points of disagreement with Dr. Czymmek's definition of the level of ordinary skill in the art?

A I'm sorry, can you say the question one more time, sir?

Q Is there anywhere in your declaration, Exhibit 2024, where you identify any points of disagreement with Dr. Czymmek's definition of the level of ordinary skill in the art?

A Nothing immediately comes to mind, in answer to your question.

Q Now, in 2015 -- let's get the priority date right so we know, just confirm what that is. I want to say November, but I want to just double-check.

Okay. You understand the priority date for the '554 patent is November 2015?

A Yes, I do.

Q Now, in November 2015, were people of ordinary skill in the art aware of the concept of stacking focal claims to do 3D microscopy?

A What I would say is that, in general, the idea of taking a stack to acquire a volume was known. But of course in particular, and with reference to our discussion here, what was not known is the know-how to any multiplexed RNA environment obtained axial coordinates, as I discussed at length in my declaration.

You know, the part that is specific to this patent, namely, element E of the '554 patent, determining the three-dimensional positional information of said one or more nucleic acid molecules in the context of the entire claim 36.

Q Okay. Now, you'll get a chance on redirect to go through that stuff. But what I want you to do is just answer my question, okay?

Do you understand that?

A I understand about what you're asking of me, yes.

Q Okay. So, in November of 2015, would a person of ordinary skill in the art know how to focus light source in a single plane?

A You have to be a little bit more specific. When you say "focus light in a single plane," do you mean at the exclusion of all other planes?

Q I mean, obviously, there can't be total exclusion. But would a person of ordinary skill in the art know that you focus light source to beyond a single plane?

A A person -- a POSA would have known that there were certain techniques that would preferentially focus light in one plane relative to others.

Q And what were those techniques?

A One example of such a technique is light sheet microscopy.

Q Are there any other examples that were available in 2015 for focusing light in a single plane?

A Another example might be total internal reflection fluorescence microscopy, which confines light to one plane.

Q Any other examples?

A Again, depends on exactly what we mean by, I think, focusing light. So, how much exclusion we're talking about. Two-photon microscopy would be an example that is -- better focuses light in one diffraction limited area than, say, widefield microscopy. So depending on exactly what you're talking about, a POSA might have known there were different techniques that are better or worse suited and with various trade-offs therein for focusing light and taking Z stacks and determining the three-dimensional positon information of nucleic acids.

Q A person of ordinary skill in the art

would have understood those techniques and trade-offs in November 2015?

A Again, you're asking a very general question. So as I point out in my declaration, it would not have been obvious to say, a POSA, knew how to do what is described in the '554 patent in claim 36E, in the context of the entire claim.

Q Okay. But I was asking something general. Is it accurate that in 2015, a POSA would have known that there were different techniques that are better or worse suited with various trade-offs for focusing light and taking Z stacks in three dimensions?

A I think that's a fair statement. In general, a POSA would have known that such techniques existed.

Q Okay. Was a person of ordinary skill in the art able to quantify how effectively one is focused in illumination source in a particular focal plane?

MR. HOLMAN: Objection. Form. Foundation.

A What do you mean by "effectively focused"?

Q How well.

A If you're asking whether a POSA would have known the difference between, say, a widefield microscope and a focal microscope, that would have been general knowledge by 2015.

Q I'm asking something different. I'm asking something -- would someone know how to quantify how good of a job they were doing with a particular microscopy modality of focusing light in a single plane?

MR. HOLMAN: Objection. Form.

A Well, I think that depends on things like the sample, what the sample consists of and what kind of readout a POSA would have had for assessing how good their technique was. So you're asking a very general question, but it's hard for me to give you general answers.

Q In November of 2015, what were people of skill in the art able to achieve in terms of focusing light in a single plane?

A Well, a POSA would have known, in 2015, that there are techniques, like widefield microscopy, that don't focus light, at all, in a single plane. Or light sheet microscopy that, in some contexts, could focus light in one plane with various trade-offs. A POSA would have known that, for example.

Q Okay. Now, could widefield microscopy be used with the system of claim 36 of the '554 patent?

A Well, if a widefield microscope didn't violate any of these other criteria or didn't otherwise come in conflict with any of the elements of claim 36, what I can say is that there's nothing -- there's nothing in claim 36 that refers to widefield microscopy one way or the other.

Q November 2015, would a POSA know that you could use widefield microscopy to implement the system of claim 36?

A Well, depends on, you know, exactly what the goals of the said microscopist are and

what the sample we're talking about is.

Q So with certain samples and with certain goals, you could implement the system of claim 36 using a widefield microscope?

MR. HOLMAN: Objection. Form.

A I don't think that's -- well, I don't think that's quite right in the sense that, you know, with a sufficiently 3D sample, for example, a widefield microscope would be a poor choice to implement the system of claim 36.

Q I don't think you listened to my question.

You would agree that certain samples and for certain goals, you can implement the system of claim 36 using a widefield microscope?

MR. HOLMAN: Objection. Form.

Q Note that I qualified my question to limiting it to certain samples and certain goals?

MR. HOLMAN: Objection. Form.

A I don't think it's just a matter of certain samples and certain goals. Really, a way that I read claim 36 is as an integrated system.

A widefield microscope would have to satisfy every one of these elements to be in accordance with claim 36.

Q Let's talk about the modality, the microscopy modality of widefield microscopy. You agree that that microscopy modality could be used to implement the system of claim 36, fair?

A Well, not necessarily. Depends on, for example, the nature of the sample. You know, a widefield microscope may not be successful at all in implementing the system described in claim 36, if the sample possesses a density that is too great, if a sample is too 3D because a widefield microscope would photobleach the sample, if there was too much autofluorescence, too much background. As I describe at length in my declaration, there are a number of factors that are extremely relevant for the success of claim 36, which Dr. Czymmek doesn't acknowledge.

So I don't think it's accurate to say that a widefield microscope couldn't generate the claim of 36 of the '554 patent.

Q I never -- you've got to make sure you listen to my question, okay? I didn't say in general and in all situations, okay? I'll try to narrow it for you.

Do you agree that with certain samples and certain situations, you could use widefield microscopy to implement the system of claim 36, right?

MR. HOLMAN: Objection. Form.

A I would agree that there may exist some kind of sample and there may exist a set of circumstances around the widefield microscope whereby you would not result in total failure in trying to implement claim 36.

Q Okay. And what are the types of samples and circumstances where widefield microscopy would be an adequate choice?

A I can give you examples that would definitely not work. For example, the kind of sample disclosed in MERFISH and in Chen would not be a good match for this.

So, I'm struggling to give you an exact

example because the nature of my answer really depends on a whole bunch of things about the sample and characteristics of the sample, as I described in my declaration, including the characteristics described -- that I mentioned before, such as the autofluorescence, such as the signal density, such as the resolution required of the sample.

So, if you're asking, you know, does there exist some sample that bypasses all of those things, maybe the answer is yes. But I can't readily think of such a sample.

Q Okay. I can't -- sitting here today, you can't think of any sample or any set of circumstances where widefield microscopy would be suitable modality for implementing claim 36?

MR. HOLMAN: Objection. Form.

A I mean. The one sample that might come to mind might be a single nucleic acid molecule. If there was just one nucleic acid molecule and the widefield microscopy was properly equipped and there was no autofluorescence, there was no

background, the signal to noise ratio wasn't a problem, in that case, you might technically be able to satisfy all of the requirements of claim 36.

Q And would that be for volumetric imaging?

A Again, if there was one molecule and the widefield microscope was suitably equipped, then you might be able to pin down the three-dimensional positional information of that one molecule.

Q When you say "one molecule," do you say one individual molecule or one species of molecule?

A The example that I have in mind, which, again, I feel obligated to point out, is really not germane to any of my declaration or Dr. Czymmek's declaration or my rebuttal to Dr. Czymmek's declaration, would be a single molecule.

Q Okay. Now, November of 2015, were people skilled in the art aware of different

microscopy modalities for doing 3D microscopy?

A Again, as I said before, in general, a POSA would have known that there are different 3D microscopy methods that may be appropriate for different applications. But they would not have known how to implement the system in claim 36.

And in particular, as I said in my declaration, it would not have been possible to come up with a system that combined Chen and Shen and Cai in such a way as to satisfy claim 36.

Q That wasn't my question. You know, at some point, I'm going to go to the board, but I need you to just answer my question. It's been a little too much adding additional material.

Do you understand?

A Yep.

Q I want you to answer my question as directly as possible. Can you do that going forward?

A Sir, I understand what you're saying.

Q I just want you to confirm.

Will you agree, going forward, to

answer my questions as directly as possible? Will you agree to that?

A Sir, I'll answer your questions as directly as I know how.

Q You're a pretty smart guy, so I think you know how to answer my question directly. So I'll ask my question again.

In November 2015, were there different microscopy modalities available for 3D microscopy?

Answer that as directly as you can.

MR. HOLMAN: Object to form.

A You're asking a very general question, so I'm give you a general answer. In general, a POSA would have known that there are 3D microscopy techniques.

Q What were some of the 3D microscopy modalities that were available in November 2015?

A One example would be widefield microscopy; another example would have been focal microscopy; another example would have been light sheet microscopy.

Q Have you ever heard of something called

HILO microscopy?

A I have heard of HILO microscopy.

Q And was that a microscopy modality that could be used in 3D, in 2015?

A Well, depends on exactly what you mean by 3D, sir.

Q Three-dimensional volumetric imaging.

A So, I think it's important to point out that in all of these techniques, there are different degrees of success in doing 3D imaging.

One weakness of the technique you just mentioned is that it's privy to a bunch of out-of-focus light. And I discuss, at length, in my declaration, the problems with out-of-focus lights in 3D specimens.

Q Okay. So we'll come back to that.

So let me ask this question: Would a person of ordinary skill in the art have known, in November of 2015, that there were certain microscope modalities that were better suited for 3D as opposed to 2D?

A Again, the answer depends on exactly

how you define 3D or 2D. I'm not trying to be persnickety here, it really does depend on what you mean by 3D and 2D.

Q What are the different possible definitions of three-dimensional that might fly here?

A So, we can be talking about, for example, in one focal plane, determining whether a molecule is exactly in the center of that focal plane or somewhere else. That might be one example of, you know, something that's predominantly in a 2D plane but has some variation in that plane. That would be one example where there's a subtlety. It's not so clear whether we're talking about 2D or 3D in one focal plane.

Q Okay. Is there an understanding -- how about volumetric? Do you understand that as one definition of 3D?

A I would agree that volumetric implies 3D.

Q Now, would a person of ordinary skill in the art, in November of 2015, have been aware

that there's certain microscopy modalities that are better suited for volumetric imaging?

A Well, one point I'd like to make is even the meaning of the term "volumetric" requires some context. And I'll give an example of what I mean. In Chen's MERFISH paper, the image cells, which everybody would agree would have some volume and, yet, that technique is a good example of a 2D technique, taken with a widefield microscope. So although the sample has some volume, Chen 2015 are not able to extract any volumetric information from the sample.

Q Okay. I'll try it this way: What do you understand volumetric to mean within the context of the -- let's try it this way: What do you understand three-dimensional to mean within the context of the '554 patent, claim 36?

A So, I can define it by what it isn't, certainly. So as I describe in my declaration, there are numerous examples of RNA FISH techniques, including Chen and Cai, where 2D images are shown of the molecules' position in 2D.

I would assert that there is no 3D in Chen 2015. There's no teaching of 3D because every image is a 2D image of 2D localization of molecules and nowhere in the entire paper is there any teaching about how to acquire the axial coordinates of that molecule. This would be an example of something that is not 3D but only 2D.

Q Can you be any more specific about what 3-dimensional means in the context of claim 36, the '554 patent, other than to say that it's not Chen?

A Well, the best example I could give is, you know, this sentence, or phrase, determining three-dimensional positional information of said one or more nucleic acid molecules, which is not disclosed in Chen.

Q Okay. Let me ask it this way: In November 2015, would a person of ordinary skill in the art have understood that certain microscopy modalities were better suited than others to determining three-dimensional positional information of targets?

A A POSA would have understood that some techniques are better than others for determining three-dimensional positional information.

Q And what microscopy techniques would they have known are better for that purpose?

A Is the purpose you're talking about, specifically, nucleic acid molecules or are you asking --

Q Nucleic acid molecules.

A Nucleic acid molecules.

So, it would depend on the exact example. And things like autofluorescence and density, for the kind of sample in Chen 2015, it's not obvious what technique one would have used to determine three-dimensional positional information. But if you're asking, in general, then, for example, one would have -- a POSA would have known that using a widefield microscope is likely a poor choice for 3D imaging.

Q What would be a good choice for 3D imaging?

A I mean, there are only trade-offs, you

know, because of -- the answer to your question depends on the exact sample we're talking about.

So if I don't care about photobleaching at all, then maybe confocal microscopy is a good choice. If I don't care about damaging my sample at all, then maybe two-photon microscopy would be a good choice. If I don't care about resolution or NA or magnification, then maybe light sheet microscopy is a good choice.

See, the answer to your question really depends on what trade-offs you're willing to accept in 3D microscopy, for reasons that I detail in my declaration.

Q In November of 2015, would a person of skill in the art have understood the trade-offs that would have been involved in selecting the different microscopy modalities?

A Well, a person of skill in the art would have understood that there were trade-offs.

Q And would they have understood what those trade-offs are?

A In general, a POSA would have

understood that there are trade-offs in doing 3D microscopy.

Q Okay. You just keep saying that a POSA would have understood that there are trade-offs. Would they have understood, specifically, what the trade-offs are or what they would have to give up, specifically, with each of the different modalities?

MR. HOLMAN: Objection. Form.

A If you're asking in general, again, then the answer is, yes, in general, a POSA would have understood. But if you're asking -- but specifically, maybe not.

For example, in the context of the '554 patent, and Dr. Czymmek's argument, it would not have been possible for a POSA to chain together the teachings of Cai, Shen, and to Chen so as to come up with the claim system of 36. This is an example where, you know, one would not have been able to come up, a POSA would not have been able to chain these things together. So the answer to your question depends on how general the

question you're asking.

Q Now, that was mostly nonresponsive. Again, I ask that you just answer my questions as directly as possible. You agreed to do that earlier, so I'd ask that you stick to that agreement, okay?

Now, you spent a lot of time in your declaration talking about point spread functions, right?

A Yes, I do.

Q Now, would a person of ordinary skill in the art know of ways to improve the point spread function in the sample in November 2015?

A When you say "improve the point spread function," can you be more specific?

Q I mean overcome the problems of the point spread function.

A What problems are those, sir?

Q Resolution.

A You're asking if a person would have known that there are methods to improve resolution over a standard point spread function?

Q Yes.

A A POSA would have known that there are methods that, in some contexts, can provide better resolution than what is available under a standard point spread function.

Q And what were the methods of -- what methods were available for doing that in November 2015, that a person of ordinary skill in the art would have known of?

A Well, in general, there's a broad class of methods called super-resolution microscopy methods that a POSA would have known existed.

Now, whether or not they would be relevant to actually improving resolution in practice, again, comes down to the details of what exactly we're talking about. But in general, a POSA would have known that there are classic methods called super-resolution microscopy methods.

Q Those are methods like SIM?

A SIM is one super-resolution microscopy method.

Q IPALM?
A IPALM is another super-resolution microscopy method.
Q CSLSM?
A I'm not sure what that acronym is, but okay. You'd have to give me some documentation to define what that is.
Q I said it wrong. CLSM.
A Confocal laser scanning microscopy is not considered to be a super-resolution method.
Q That's not a super-resolution? Okay.
What are some of the super-resolution methods that were available?
A For example, PALM, for example, STORM.
Q These were all available in November 2015?
A IPALM, PALM, STORM, 3D SIM were all available in November 2015.
Q Now, how about refractive index matching? How does that overcome resolution problems associated with the point spread function?

A Well, you know, a POSA would not immediately think of refractive index matching to overcome resolution. Refractive index matching is, usually, a POSA would have thought about that in a context of, say, tissue clearing.

Q Okay. If you match the refractive index of the media with your lens, there's going to be less refraction, right?

A What I would say about that is that if you refractively match the index, then you might recover diffraction limit revision. But in any case where there isn't refractive index match, the resolution would be worse at the point spread function.

Q So, where you have the refractive index matching you can increase your resolution?

A It's not quite correct. Rather, I would say in the best-case scenario, if you are correct about refractive index matching, you would get to the point spread function. The sense in which you're using the term, I think, increased resolution, I think, is beyond the diffraction

limit. So you cannot get beyond the diffraction limit by changing the refractive index of the media.

Q But you can get to the refraction limit?

A You can get to the diffraction limit.

Q Now, how about using deconvolution methods to improve resolution? Were people skilled in the art aware of that in November 2015?

A People would have known that deconvolution microscopy existed in 2015.

Q And those methods are based on modeling the point spread function using some mathematical model?

MR. HOLMAN: Objection. Form.

A Those methods assume knowledge of the point spread function. And they use that in order to, again, get to the diffraction limit.

Q And these were available in November 2015?

A Some kinds of deconvolution were available in 2015.

Q Now, how about expansion microscopy? That's a technique for improving resolution as well, right?

A Expansion microscopy is a technique for improving resolution. Regarding whether that was available in 2015, you would have to check the reference.

Q Do you know if it was available in 2015 or not?

A Without seeing the reference, I can't remember.

Q Now, one of the other things you identify as a challenge with high density of targets -- well, let me take a step back. One of the other challenges you identified with one of the three-dimensional imaging is that there's potentially a high density of targets.

And you say it's a bigger problem in 3D than it is 2, right?

MR. HOLMAN: Objection. Form. Foundation.

A I discuss signal density, and I discuss

axial resolution. You'd have to point me to the exact place you're discussing, sir, about where I mix the two together. You'd have to help me find.

Q Just let me ask you. Is it true that with 3D, density of targets is a bigger issue than with 2D imaging?

MR. HOLMAN: Objection. Form.

A I would say that in general, all of the problems that I outline regarding signal density, regarding background, become more problematic in 3D than 2D.

Q Okay. Were people of skill in the art, in 2015, aware of the option of using multiple colors for different targets to overcome challenges with target density?

MR. HOLMAN: Objection to form.

A Different colors of targets? Sorry, I'm not sure what you're getting at there.

Q Where you use -- in a situation where you're trying to analyze multiple targets and the density of those targets might be high, did people know, in 2015, that one thing you could do is use

different fluorophores for the different targets and interrogate the different targets in serial fashion?

A I think I -- I think I understand what you're getting at here.

You mean if you have, for example, two molecules that are separated by less than a fraction limit, if you label them with two different dyes, you can resolve them? Is that what you mean?

I'm trying to figure out what you're talking about here.

Q Interrogate them serially.

A Interrogate them serially? And what does that have to do with anything?

Q Well, you wouldn't be detecting the light from the two targets at the same time.

A Why is that?

Q Because you would be using one fluoro for the first and then detect that one, and then use a different fluoro for the next one and then detect that one.

MR. HOLMAN: Objection to form.

Q Or maybe different excitation wavelengths?

MR. HOLMAN: Objection. Form.

A I'm still not quite sure what you're getting at. It's clear that if you have two different fluorophores, you can, with the right imaging, detect them at the same time. I'm not sure, again, what you're driving at here.

Q And that was known in November of 2015?

A What was known?

Q That if you have to two different fluorophores, you could detect them at the same time?

A In some circumstances, it was known that if you have two different targets with two spectrally distinct fluorophores, you could, in principle, direct them at the same time.

Q And you could do that with increased resolution over the situation where you're trying to detect the two targets at the same fluorophore at the same time?

MR. HOLMAN: Objection. Form.

A Depends. The answer to that really depends on how many targets we're talking about. Are there only two targets? How far apart are they? How much signal do they have? I can't, in general, answer your question.

Q Can you say, one way or the other, whether in November 2015, people of skill in the art understood that they could overcome challenges with signal density by increasing the number of fluorophores that they were using to interrogate the different targets?

Could you say whether people of skill in the art understood that?

MR. HOLMAN: Objection. Form.

A I can't -- I can't really say, definitively, whether people, in general, understood that because the answer to whether or not that was possible really depends on the context. I'll give you an example.

In the case of the MERFISH paper, there were so many targets that the concerns that I

outline in my declaration are real problems for using spectral separation to resolve multiple targets. Of course, if we're talking about the highly artificial case of just two targets, yes, a POSA would have known, in theory, that if you had just two targets that are isolated from everything else, i.e., there isn't anything else, then, in principal, you could use them. But you see how -- I'm not trying to be elliptical. The answer to your question really depends on exactly what we're talking about.

Q Were there situations where a person of skill in the art would recognize that, yes, by going to an increased number of colors, we can detect more targets and avoid the problem with signal density?

Did people understand that concept, generally, that that was something you could try?

MR. HOLMAN: Objection. Form.

Q Or do you not know?

MR. HOLMAN: Same objection.

A In general, people knew that spectral

separation is one strategy for improving resolution. But whether or not this would be successful, whether or not they would have been motivated to try, these are contingent on the exact scenario of your question.

Q Let's go to paragraph 24 of your declaration. And here, you show these point spread functions for these different microscopy techniques?

A Yes.

Q Okay. And these are all techniques that were available in November 2015?

A Yes. I agree with that statement.

Q And iPALM, was that a method that was being used in November 2015 for 3D imaging?

A In extremely narrow contexts, iPALM was used for super-resolution imaging. The more general point, again, that I would make is that these techniques existed, but a POSA would have known that the application of these techniques is extremely contingent on the sample. This is why, for example, in this reference, which I

co-authored, I outline when and when these techniques -- when these techniques are appropriate and when they are not appropriate.

Q Now, is it, in general, true that the microscopy modality you're going to choose is going to depend on the sample type?

A In general, that is true.

Q Okay. And in November 2015, that was something that a person of ordinary skill in the art would have understood?

A A person would have understood, in 2015, that the kind of imaging technique you use would have depended on the kind of sample you pick. But what gives me pause here is that Dr. Czymmek didn't understand this distinction in his declaration because he claimed one could have applied techniques from Cai in order to get at claims 36 in Chen, showing that he really doesn't understand this point.

So a POSA would have understood that, in general, these techniques existed. But it is not obvious, in all cases, which technique to use,

as evidenced by Dr. Czymmek's declaration.

Q Would a person of ordinary skill in the art, in November of 2015, had an understanding of which microscopy modalities were appropriate for different kinds of samples or would they have just been walking around in the dark?

MR. HOLMAN: Objection. Form.

A You're making an assumption that I don't necessarily agree with. I think there's a lot of room between walking around in the dark and knowing exactly what technique to use. So it's not as simple as you're making out. Again, a POSA would have known that such techniques existed, generally, but it's far from obvious which technique to use for a particular situation, like the case of multiplex MERFISH, which Dr. Czymmek takes up in his declaration.

Q Now, let me ask the question again. Would a person of ordinary skill in the art have known, you know, had some basic understanding of how to select a microscopy modality for a particular sample type?

A In general, a POSA would have known one class of techniques would have been more suitable for this class of samples. But a POSA would not have known, for example, in this particular example, they would not have necessarily known which sample technique was best, even if it was the best sample technique. The best evidence I have of that is exactly as I described in my declaration. Dr. Czymmek erred when trying to show that the combined limited technique from one method on top of another method in order to provide 3-dimensional imaging of the kind described in the '554 patent.

Q Now, in the '554 patent, is there any particular microscopy modality that's recommended for use with the claims?

A So what I would say about that is that the '554 patent describes many techniques in many different embodiments that are conceivably useful in the case of this patent. But they're conceivably useful in the same context in which a POSA would have known the techniques are

conceivably useful. That's what I say about that.

Q And this was in November 2015? Or earlier, right?

A Certainly, in November 2015, the '554 patent describes 3D imaging techniques that are incorporated into their patent specification.

Q Now, you've said, in your previous answer, that the '554 patent describes many techniques that are conceivably useful, and you said they're conceivably useful in the same context which a POSA would have known the technique is conceivably useful.

What did you mean by that?

A Well, what I mean is that the '554 patent describes 3D imaging techniques that are useful for imaging 3D samples. But I guess what I'm getting at is, again, the specific 3D imaging technique that one would have wanted to use really depends on exactly what specimen we're talking about. And so, in order to get that, you would have to have a discussion about what sample, in particular, we're talking about. And for the

class of samples that Dr. Czymmek takes up, as I describe in my patent, it's not obvious which of these techniques that are in, for example, this Figure 1019 one should use. In fact, Dr. Czymmek errs, he mistakenly conflates multiple 3D imaging techniques in an attempt to say that one could have come up with the '554, claim 36.

Q You agree that in November 2015, a person of ordinary skill in the art would have had a good idea which microscopy modality to select for the particular sample he or she were looking to analyze, right?

A Again, what I've said is that a POSA would have generally known that there are different 3D imaging techniques. And they might have had some general understanding of the domain in which a particular technique is appropriate. But they would not have known, specifically, for the case that Dr. Czymmek brings up, which technique to use.

Q And the case you're thinking of is 3D MERFISH?

MR. HOLMAN: Objection. Form.

A I bring up 3D MERFISH in the context of Dr. Czymmek, sir. That Dr. Czymmek asserts that one could get to something like 3D MERFISH by combining Chen, Cai, and Shen.

Q What I'm asking you is, you said they wouldn't have known what particular technique was appropriate, specifically, for the case that Dr. Czymmek brings up. What is the specific case that Dr. Czymmek brings up that you think a POSA wouldn't have known what to select?

A Yeah, so, the clearest I can be here is on paragraph 76, the first sentence, where I say according to Dr. Czymmek, the POSA would have been motivated to modify Chen's 2D MERFISH imaging setup in view of Shen and Cai's discloses to create a volumetric imaging system for 3D MERFISH.

That's exactly the system in which I think Dr. Czymmek gets it wrong.

Q Okay. Your testimony is that a person of ordinary skill in the art, in 2015, looking at the Chen MERFISH paper, would have had no idea

what microscopy modality might work to extend MERFISH to 3D; is that right?

MR. HOLMAN: Objection. Form.

A Sir, my testimony is exactly the first sentence of 76. That's the testimony that I have in this declaration, sir.

Q Okay. Is it your opinion that the person of ordinary skill in the art in 2015, looking at the Chen MERFISH paper, would have had no idea what microscopy modality might work to extend MERFISH to 3D?

Is that your opinion?

MR. HOLMAN: Objection. Form.

A As I said before, the POSA would have known, in general, that there are different 3D imaging techniques with different domains of expertise. But it is not obvious how to take the MERFISH paper, in light of Shen and Cai, to 3D. This wouldn't have worked, as described by Dr. Czymmek, for the reasons that I describe in my declaration.

Q In November 2015, were you someone of

ordinary skill in the art?

A I think I was somebody with more than ordinary skill in the art in November 2015.

Q Now putting yourself in the shoes of someone of ordinary skill in the art in November 2015, having read the Chen MERFISH paper, what microscopy modality would that person have been motivated to try in order to extend that to 3D?

MR. HOLMAN: Objection. Form.

Q Would they have just said I'm never going to try it --

MR. HOLMAN: Objection. Form.

Q -- it's a crazy thing to do?

A It's not that they would have said it was a crazy thing to try, but they would have run up against many of the problems that are encapsulated in Dr. Czymmek's statement.

Q Okay. So what microscopy modality -- they wouldn't have thought it was a crazy thing to try, so they would have tried it. What microscopy modality would they have been motivated to try?

MR. HOLMAN: Objection. Form. Scope.

A I have no idea what a POSA might have tried.

Q Wait. Hold on. Stop. You're the expert here on obviousness. You're supposed to be presenting opinions on that. Now, if you want to stick with that answer, that you have no idea, that's fine. But I just want to remind you, your role here is provide opinions precisely on that.

So let me go back and ask my question here.

MR. HOLMAN: Counsel, before you begin your question, please, don't interrupt the witness. Let him, please, complete his answer. Thank you.

Q So, let me go back to my question.

What microscopy modality would a person of ordinary skill in the art, in November of 2015, have been motivated to try in extending the Chen MERFISH paper to 3D?

MR. HOLMAN: Objection. Form.

A The problem with your question, sir, is

that as I describe in my declaration, this is a sufficiently complicated sample that any 3D imaging modality, that we've discussed so far, would encounter trade-offs and problems. And many of those trade-offs and problems are discussed in my declaration here. After all, Dr. Czymmek, it's my opinion that Dr. Czymmek erred, and Dr. Czymmek is a POSA. Dr. Czymmek erroneously considered that one could have just combined these references in a way in which to get to 3D. And as I say, Dr. Czymmek is not correct about that. So for that reason, I'm disputing, a little bit, the tenor of your question. I don't think it's obvious what a POSA should have done or not. Dr. Czymmek came up with an opinion that I have picked apart for the reasons that are in my declaration, precisely because of these trade-offs in 3D imaging that we've discussed.

Q So in your view, November 2015, a person of ordinary skill in the art who was considering applying 3D -- applying 2D MERFISH in Chen 3D, they wouldn't have had any idea what

microscopy modality to try, it just would have been flunks?

MR. HOLMAN: Objection. Form.

A I think it's not obvious what 3D imaging technique to try. But as I said before, a POSA would have known, as described in the reference on point spread functions that we just discussed, FISH and all, that there are these different domains in 3D imaging techniques generally apply.

Q What are the different options that would have been available in November 2015? What are the choices?

A Well, a POSA would have known that, generally speaking, there would be techniques like widefield microscopy and focal microscopy, light sheet microscopy, structured illumination microscopy, a POSA would have known that such 3D imaging techniques existed.

Q Can you think of any other options?

A 3D SIM would be another example.

Q Any others?

A I mean, a POSA would have known about the existence of iPALM, PALM, and STORM. But as I think we've discussed, these techniques come with a hefty -- with hefty caveats of their own in trade-offs. So, again, I guess my answer remains that a POSA would have known that these, generally speaking, 3D imaging techniques exist. But as for Dr. Czymmek, it would not have been obvious how to bring those to bear on this patent to arrive at the claims in the patent.

Q Which ones of the options would a POSA have been most likely to try?

MR. HOLMAN: Objection. Form.

A Honestly, I'm not sure. I would have to really think about that, sir. I don't have a ready-made answer at my disposal with a magic bullet here because I don't think it's obvious that there is a magic bullet. For the reasons that I describe in my declaration, the 3D imaging is nuanced. And then when we're talking about resolving point sources, there are other criteria that come into play, like signal density, other

fluorescences, background, photobleaching. So there's no panacea that gets you to the ideal answer.

Q It depends on the sample?

A That's what I've said before and what I maintain. Depends on the sample.

Q And I think as you said before, a person of ordinary skill in the art would, in general, have an understanding of how to select a microscopy modality for the sample, fair?

MR. HOLMAN: Objection. Form.

A In general, a person skilled in the art would have known that there are different 3D imaging techniques with different strengths and weaknesses for different classes of samples. That as soon as we talk about some particular sample, it's much less obvious that a POSA would have known which technique to select. And the best evidence that I have for that is my refutation of Dr. Czymmek, who is a POSA, and, yet, erred in his conclusion about what techniques could have been combined to achieve results similar to those

described in the '554 patent, claim 36.

Q Now, had you heard of Dr. Czymmek before this case?

A I had never heard of Dr. Czymmek before this case.

Q Okay. Now, in November 2015, what were the techniques a POSA would have been aware of for improving axial resolution of 3D microscopy?

A For improving axial resolution, a POSA would have known that 3D SIM is a technique for improving resolution that is completely inconsistent with the idea of imaging single molecules, which is why it's not been applied to that. A POSA would have known that PALM -- that iPALM was a technique for improving resolution, but it's only ever been applied to imaging samples that are extremely thin, much less their cell and thickness. A POSA would have known that PALM and STORM are techniques that, in principle, could have improved 3D resolution but, in practice, it would depend on the nature of the sample, the choice of the dyes, the contrast ratio of the

dyes, and so on or so forth.

So a POSA would have known that there are techniques from improving 3D resolution, and, again, with different strengths and weakness, that may or may not apply to a sample. It really depends on the sample under question. And it would have probably required experimentation to figure out if they were appropriate to a given sample.

Q Now, with regard to axial microscopy, a person of ordinary skill in the art would have known about deconvolution, right?

A As I think I said before, a person skilled in the art would have known that deconvolution microscopy could be used to get you to the resolution but not exceed the resolution limit.

Q So it's something someone could try to improve resolution with. You would have limits, it would limit it to the diffraction of it, but if you were not having the diffraction limit, you could use the convolution to get you to the

diffraction, right?

MR. HOLMAN: Objection. Form.

A In principle, in an ideal sample, deconvolution can be used to obtain diffraction limit resolution, is what I'd say about that.

Q And there was publicly available software that was commercially available off the shelf or during deconvolution in 2015, right?

MR. HOLMAN: Objection. Form. Foundation.

A I think you'd have to remind me on what those software packages are. So I couldn't say, precisely, what you're talking about without a reference.

Q Do you know if there was publicly available commercial software for deconvolution in November 2015? Do you know one way or the other, as a person of not just ordinary skill in the art but beyond ordinary skill in the art?

Do you know?

MR. HOLMAN: Objection. Form.

A Are you talking about publicly

available or commercially available?

Q Commercially available. That's the same thing, isn't it?

A Okay. So from what I remember, there was, for example, a software package called Huygens, which is a commercially available deconvolution software package that may have been used prior to 2015. But I'm relying on my memory here, and I really don't have the names of all these things at my fingertips. Nor would I be unable -- nor would I be readily able to say that such software would have been applicable, in general, to massively multiplex MERFISH data. This is something that even I, somebody more than skilled in the art, would have to do a study on to be absolutely sure of.

Q On that note, what is the minimum number of targets a POSA would understand the MERFISH method, set forth in Chen, could be used for?

A Do you have the MERFISH paper?

Q Yes. Here you go.

(NanoString Exhibit 1003 previously marked for identification and retained by counsel.)

Q It's Exhibit 1003. Again, the question is, what's the minimum number of targets that MERFISH, as set forth in Exhibit 23, could be used for?

A So I find your question a little odd in the sense that a POSA would have known that the goal of MERFISH is massive multiplexing in a sense beyond what was known at the time.

So, I don't have an exact answer because -- for that reason. But, you know, if you're asking me for a number, then, you know, I can simply read what is the abstract here, which is that we demonstrated the imaging of 100 to 1,000 distinct RNAPCs. In that sense, a hundred is less than a thousand.

That is a minimum by the authors of the paper themselves.

Q Would a person of ordinary skill in the art understand that you could use MERFISH for less

than a hundred targets?

MR. HOLMAN: Objection. Form.

A That's, again, an odd question because a person skilled in the art would, then, wonder why one is using MERFISH at all, given the prior art. So the whole goal of MERFISH, as I discuss in my declaration, is to go beyond state of the art and the POSA would have understood that point, that MERFISH teaches beyond the limited multiplexing available in earlier art.

Q Why don't you go ahead and answer the question now.

Would a person of ordinary skill in the art know that you could use MERFISH for less than a hundred targets?

MR. HOLMAN: Objection. Form.

A I think my answer is the same. That you're implying that -- you're implying that a person would use MERFISH for some small number of targets, and that's a premise I don't necessarily agree with on the basis of what I understand about MERFISH.

Q Yeah. I'm just asking a question. I'm not asking whether it's something a person of ordinary skill in the art would do, I'm asking if they could do it.

Could they do MERFISH on less than a hundred targets. Could they?

MR. HOLMAN: Objection. Relevance.

Q Or is it impossible, it's not going to work?

MR. HOLMAN: Objection. Relevance. Form.

A I mean, I can't argue that it is impossible. I don't have that information to do MERFISH with less than a hundred targets.

Q You don't know, one way or another, whether you could do MERFISH with less than a hundred targets, as someone of ordinary skill in the art who has read the paper, who has presented opinions on nonobviousness, you can't say, one way or another, if someone of ordinary skill in the art could do MERFISH with less than a hundred targets?

MR. HOLMAN: Objection. Form. Relevance. Scope.

A Well, another reason that I think the answer to your question isn't obvious is that the authors of the MERFISH paper, themselves, point out that there are certain RNA targets that are not assessable with MERFISH, high-density targets. So, actually, it isn't obvious that you could, in general, do MERFISH with less than a hundred targets. I think it depends on what targets we're talking about.

Q Okay. Would a person of ordinary skill in the art know that if you want to adapt MERFISH, as set forth in Chen, and take it to 3D, you might have to decrease the level of multiplexing?

MR. HOLMAN: Objection to form.

A I'm not sure about that, sir. I don't know whether a person would have realized they would have decreased -- they should have decreased the level of multiplexing or not. Because that would imply that they would have -- in some ways, that would imply that they would have done the

experiment and determined, as I pointed out in my declaration, that signal density would be issue, that autofluorescence could be an issue, that resolution could be an issue.

A little bit of a tautology, what you're asking me. The answer is, I don't know.

MR. HOLMAN: Do you want to break for lunch soon?

MR. WALTER: Yeah, let's do that in a few minutes.

Q You mentioned autofluorescence. In November 2015, were techniques available for reducing autofluorescence that people of ordinary skill in the art were aware of?

A In November 2015, techniques were available for decreasing autofluorescence in some samples with some instruments and with caveats to using those techniques.

Q And those were things like using quenchers?

A I'm not sure what a quencher is, sir. I don't know if you can define that or provide a

reference.

Q Have you ever heard of sodium borohydride being used as a reagent to address autofluorescence?

A I have heard of that, sir.

Q And that was something people of ordinary skill in the art knew of in November of 2015?

A Okay. If you say so. Yeah, I'd have to verify that point. I'm not entirely sure, but I can say that I have heard of sodium borohydride being used as a quencher.

Q For autofluorescence, right?

A Well, it depends on what kind of autofluorescence we're talking about and what kind of sample. You wouldn't, in general, use sodium borohydride for all kinds of autofluorescence quenching.

Q Of course not. I'm not suggesting that. I'm suggesting that people knew that was one option you could pursue for addressing autofluorescence, right?

A Depending on the sample, I would agree, yes. Depending on the sample. But not in general. You wouldn't, in general, use sodium borohydride for autofluorescence in all samples, in all microscopes.

Q How about Sudan Black? Is that another type of chemical for addressing autofluorescence?

A I've heard of Sudan Black. Whether or not it can be used for autofluorescence, I don't have an opinion on. I don't know.

Q What other techniques were known in November 2015 for overcoming autofluorescence?

A Well, one technique described by Dr. Czymmek is clarity for brain slices. But of course, as I point out in my declaration, that technique does not apply to the goal of 3D MERFISH, as described by Czymmek and my declaration. Because such techniques, while they were known, were also known to involve microscopes that were opposed to the kind of microscope that we had seen in Chen 2015.

Q What were some of other methods that

you would have been aware of in November of 2015 for addressing autofluorescence?

A Well, one technique that I know about that was used for autofluorescence is just bleaching of the sample. So if you bleach in the autofluorescence window, if you could somehow do that, then you could suppress autofluorescence. Of course that also requires knowledge of the sample and what the right regime is in which to do the bleaching.

Q In 2015, was it known that certain samples were more easily analyzed than others using 3D microscopy?

MR. HOLMAN: Objection. Form.

A What do you mean exactly by "certain samples"?

Q Was it known in 2015 that thick samples were more difficult to 3D image than thin samples?

A In general, a POSA would have appreciated that, although -- yeah, I think that's a fair statement. In general, a POSA would have realized that a 3D sample is more difficult than a

2D sample. But I want to put a caveat in there because we talked about iPALM earlier. IPALM is an example of a technique that is used on extremely thin samples to obtain some 3D information. It's, essentially, 2D, the samples in iPALM. Yet, a POSA would have realized iPALM is an incredibly difficult technique to pull off. So, maybe generally I agree with you, but you would have to be specific about which case we're talking about to get that assertion.

Q Were researchers in 2015 doing 3D microscopy on single cells?

MR. HOLMAN: Objection. Form.

A There were some researchers in 2015 that, for some samples, were doing 3D microscopy. Nobody was doing, of course, 3D MERFISH in 2015.

Q Now, were those experiments on single cells, were those important 3D microscopy experiments that you cared about or motivated to perform?

A What do you mean by "important"? I have no idea what people thought was important in

2015 --

Q Really?

A -- in 3D samples.

Yeah, you're asking me in general, you know, are these experiments important? I mean, it depends on the goals of the investigator how important it is, right?

Q You don't have any idea what the goals of the investigators were in 2015?

A I mean, in general? I mean, there must have been tens of thousands of investigators in 2015. I don't know what all their goals were.

Q Okay.

MR. HOLMAN: Derek, are you ready for a break?

MR. WALTER: Not quite.

Q You agree that 3D microscopy on a single cell, that might be something that's easier to do than 3D microscopy on a big, thick sample composed of multiple layers of cells, right?

A Well, it depends on the samples. You could have cells that are incredibly packed with a

dense fluorophore that make them really difficult to resolve anything in 3D, for the reasons that I described density in my application.

Conversely, you could have a large 3D sample with, say, one molecule in the entire sample, which might be easier.

So depends on the sample.

Q You agree that 3D imaging of a single cell, that's within scope of the claims of the '554 patent, right?

MR. HOLMAN: Objection. Form.

A 3D imaging in a single cell within the scope of the '554 patent? Yes, I agree with that.

Q And would you agree that, you know, a certain cell types and with certain numbers of targets, these types of 3D microscopy experiments were easier to do than thick samples that were composed of layers and layers and layers of cells?

MR. HOLMAN: Objection. Form.

A I think my answer has to be the same. That we need to talk about, like, what those 3D samples are with layers and layers and layers of

cells. What's labeled; how dense the label is; how much autofluorescence there is.

I mean, it's not the case that universally imaging one cell is easier than imaging a tissue, which is, I think, what you're implying.

Q Okay. Is it, in general, the case that imaging one cell is easier than imaging a tissue? Would you say that?

A Generally speaking, I would agree with that statement.

MR. WALTER: Okay. Let's go ahead and take a break.

(Recess taken from 12:42 p.m. to 1:18 p.m.)

BY MR. WALTER:

Q All right. Dr. Shroff, do you recall any description of the '554 patent about how to overcome a potential problem of signal density becoming too high?

A The thing that comes to mind are the sort of super-resolution microscopes that are

disclosed, for example, column 6, lines 5 through 20. That would be an example of the kind of super-resolution microscope we discussed earlier that generally improves the resolution.

Q Okay. And those are prior art methods that were available going back to 2008, right?

A Yes.

Q Are there any descriptions of the '554 patent about any new methods to overcome the problem of signal density becoming too high, that you're aware of?

MR. HOLMAN: Objection. Form.

A What do you mean by "new methods"?

Q Any methods that were not in the prior art as of November 2015.

A How could they be in the patent if they weren't -- I don't understand. I mean, newer than 2015, but the '554 patent date is 2015.

Q I didn't say that. I didn't say that at all.

Methods that are new in the '554 patent.

A New relative to?
Q The prior art.
A What date specifically?
Q Prior to the filing date of November 2015.
A Ah, okay. Thank you. So just to clarify, you're asking me if the '554 patent discloses methods for addressing signal density that were published after November 2015?
Q No. I'm not asking that at all.
A Okay. Sorry. That's what it sounds like.
Q No. I'm asking if the '554 patent includes any methods for overcoming signal density that were not part of the prior art?
MR. HOLMAN: Objection. Form.
A Prior art --
THE WITNESS: Sorry.
A Prior art relative to?
Q Do you know what prior art is?
A I know what prior art is, yes.
Q What is prior art?

A Prior art -- well, you have to talk about prior art relative to something, right? Prior art, in general, can be relative to anything.

So what date are you referring to?

Q In this case, we're talking about the prior art relative to the '554 patent?

A Oh, okay. So we're talking about before 2015. You're asking me if there are methods that are disclosed by the '554 patent after 2015?

Q No. That's not what I'm asking you.

A Okay.

Q I mean, I've never had a problem with this kind of question before. It's, frankly, pretty straightforward.

A Sorry to hear that.

Q I'm asking if the '554 patent purports to describe any new and inventive methods for overcoming the problem of signal density becoming too high?

MR. HOLMAN: Objection. Form.

A And, again, new and inventive, in order for me to assess that claim, I would need a date. Precise date of what was new.

Q And what I'm saying is, by sitting here today, you should know that date. That date is November 2015.

MR. HOLMAN: Objection. Form.

A So, again, I'm interpreting your question to mean, does the '554 patent have any methods to addressing density after 2015? That does seem to be exactly what you're asking. I can look for that in the '554 patent, if that's what you're asking.

Q You understand that those methods couldn't have appeared until at least November 2015, in the public, because the patent application wasn't even filed until November 2015?

You understand that, right?

A Right. I do understand that. So then you're asking me, is there prior art after that date in this document?

Q No. Because that wouldn't be prior

art, then.

A Oh, so what are you asking? What are you asking me for, then? Prior art after 2015?

Q That's not prior art. That's not prior art. If it's after November 2015, that's not prior art.

A So you're asking me is there prior art prior to 2015 that discusses signal density?

Q No, I'm not asking that. What I'm asking is straightforward.

Does the '554 patent purport to describe any methods of overcoming the problem of signal density becoming too high that are not prior art methods?

A Again, you seem to be asking me to -- you seem to be saying other methods that address signal density that are not before 2015 or after 2015. If they're not before or after 2015, then what are they -- what dates are you referring to? That will help me to answer your question.

Q There would have been new methods that were described for the first time in the

'554 patent or the applications leading to the '554 patent; that's what they would have been?

MR. HOLMAN: Objection. Form.

A New methods at the time of 2015?

Q That's the only time they could have been because that's when the patent was filed.

A Okay. So, again, you want me to go through this document and find new methods, new relative to exactly what, I'm still unsure, but the addressing of signal density prior to 2015, but new as of 2015?

Q No. The question is straightforward. It really is. Really, really is.

Do you know what prior art is, in the context of the '554 patent we're discussing? Do you know what that refers to?

A Prior art would be art published prior to November 3rd, 2015.

Q Okay. And what I'm asking is if the '554 patent describes any methods for overcoming the problem of high-signal density that are not prior art methods?

A Okay. So after 2015, by definition? By definition. We just defined that prior art had to be before November 3rd, 2015, to be considered prior art, yes?

Q Okay. But the problem is, after 2015, that doesn't mean anything. That could mean 2016. There could be something in here that's new that was filed on November 3rd, at least. So it would be new in 2015, potentially, not after 2015. It would be in 2015.

MR. HOLMAN: Objection. Form.

Q Do you understand that? When you say after 2015, that could be 2016. I'm not limiting it to 2016?

A Okay. So to be clear, you're not limiting to 2016 but it could be between November 3rd, 2015, and 2016; is that what you mean?

Q Could also be beyond November 3rd, 2015.

A Okay. I'm happy to look through this and find any articles that were published between

November 3rd, 2015, and 2016, if I can find them. Shall I do that now or -- it might be a waste of our time.

Q Let me try to ask the question a different way. This is not a hard question.

Are you aware, sitting here today, of any methods in the '554 patent that are purportedly new methods of overcoming the problem of signal density becoming too high?

MR. HOLMAN: Objection. Form.

A Again, by "new," you mean exactly from when to when?

Q I mean that were conceived of by the inventors, that they describe as something as new that they developed for the purposes of their '554 patent.

MR. HOLMAN: Objection to form.

A Again, I can try to look through the document to find dates in that period. But maybe you have an idea of what you mean and you can explain to me what methods you have in mind, then I can see if I agree.

Q Let me ask you this: Do you recall anything along those lines? You reviewed the '554 patent carefully, right?

A I did review the '554 patent carefully. And, again, if you're asking me to find references to new art, new meaning not before 2015, not prior art, but between 2015 and, let's say, 2016. I can look for those references, if you'd like.

Q I'm not looking for references. I'm not looking for citations.

A Ah, okay.

Q I'm looking for material in this specification that the inventors describe as a new method, never-before published, that relates to overcoming the problem of signal density becoming too high.

Do you remember? Do you recall anything like that?

MR. HOLMAN: Objection to form.

A The only way in which I can answer your question definitively, sir, is if I knew the dates of said work because you've categorized them as

not prior art. But you also said it could be any time after November 3rd, 2015.

So either we can look through this document and find articles like that or you can try to spell out exactly what you mean and I can see if I agree with that.

Q This is nonresponsive. This is nonresponsive. Dr. Shroff, this is not right. This question is clear and it's fair.

And I think you're obfuscating now. This is a problem.

A It's not clear to me, sir, for the reasons that I've stated.

Q Okay. All right.

Is there any written description in the '554 patent, that you recall, where the inventors described a new method for overcoming the problem of signal density becoming too high?

MR. HOLMAN: Objection to form.

A My answer's the same, sir.

Q Which is what? You don't know what new means?

A That's correct.
Q Okay. If I define "new" as not prior art, would you be able to answer the question?
A Are you defining "new" as after November 3rd, 2015?
Q I'm defining it as not prior art. Do you know what prior art, for the purposes of this patent?
A Prior art means before November 3rd, 2015.
Q Okay. So with that understanding, are you aware of any disclosure in the '554 patent where the inventors purport to describe a new method for overcoming the problem of signal density becoming too high, wherein by "new," I mean not prior art?
MR. HOLMAN: Objection to form.
A So now I'm looking for things that are after 2015, like I said before, because that's how I understand your question.
Sir, I can't find anything that I reviewed, in the course of my declaration, that is

after November 3rd, 2015, and, thus, by your definition, not prior art for this patent, that discloses methods of improved signal density.

Q In your review, do you recall anywhere in the patent where the inventors describe what they contend is a new method of overcoming signal density, something that they invented in connection with their patent filing?

MR. HOLMAN: Objection to form.

A Not to my recollection, no.

Q Okay. In your review, do you recall anywhere in the patent where the inventors describe what they contend is a new method of measuring point spread functions in the sample, such that they invented in connection with their patent filing?

MR. HOLMAN: Objection. Form.

A A new method of measuring point spread function, no.

Q In your review, do you recall anywhere in the patent where the inventors describe what they contend is a new method of addressing complex

non-Gaussian point spread functions, something that they invented in connection with their patent filing?

MR. HOLMAN: Objection. Form.

A I don't remember seeing that language anywhere in the patent.

Q In your review, do you recall anywhere in the patent where the inventors describe what they contend is a new method of deconvolution, something that they invented in connection with their patent filing?

MR. HOLMAN: Objection to form.

A I do not.

Q In your review, do you recall anywhere in the patent where the inventors describe what they contend is a new method of improving axial resolution, something that they invented in connection with their patent filing?

MR. HOLMAN: Objection to form.

A I do not.

Q In your review, do you recall anywhere in the patent where the inventors describe what

they contend is a new method of overcoming the problem of autofluorescence, something that they invented in connection with their patent filing?

MR. HOLMAN: Objection. Form.

A I do not.

Q In your review, do you recall anywhere in the patent where the inventors described what they contend is a new method of overcoming signal-to-noise ratio, something that they invented in connection with their patent filing?

MR. HOLMAN: Objection to form.

A I do not.

Q In your review, do you recall anywhere in the patent where the inventors describe what they contend is a new method of overcoming low signal to background ratio, something new that they invented in connection with their patent filing?

MR. HOLMAN: Objection to form.

A I do not recall that.

Q All right. Let's take a look at paragraph 78 of your declaration.

Do you contend that the use of widefield microscopy in Chen would teach away from applying Chen to 3D imaging?

MR. HOLMAN: Objection. Form.

A What I can tell you is there is no mention of any 3D localization in Chen. And that might be due, in part, to the fact they use widefield imaging. As I've discussed in my declaration, widefield imaging is a poor choice for axial result of anything. But what I contend is there is no 3D localization in Chen.

Q Would you contend that -- let's take a look at the sentence about a third of the way through the paragraph. It says a POSA would have known widefield imaging is a technique that uses, predominantly, 2D data due to lack of axial resolution in widefield imaging.

Do you see that?

A I do.

Q Do you contend that the use of widefield imaging in Chen is something that teaches away from 3D imaging?

MR. HOLMAN: Objection. Form.

A What I can contend is exactly what I wrote there. That a POSA would have known that widefield imaging is a technique that produces, predominately, 2D data. That's exactly what I contend.

Q Okay. That's right. Produces, predominately, 2D data. Does that mean to you that because widefield imaging produces predominately 2D data, a person of ordinary skill in the art would look at Chen and think that it's not appropriate for 3D?

A A person would look at Chen and think it's not appropriate for 3D because there's no mention of 3D anywhere on the paper. That's why Shen would look at Chen and not think 3D.

But it's also the case that widefield imaging for a sample, like the kind used in Chen, is a poor choice for 3D, for the reasons that I mentioned in my declaration, having to do with signal density, axial resolution, out-of-focus light, photobleaching. All of these

characteristics of this method make it -- make widefield microscopy a poor match to the problem of trying to assess three-dimensional positional information on nucleic acids.

Which is likely the reason why there is no mention of that in Chen nor in Shen.

Q Now, is widefield imaging, is that just, like, a dum-dum thing to do if you're going to try to do 3D?

MR. HOLMAN: Objection. Form.

A That's a gross generalization. I mean, it really depends on what your goals are in trying to use widefield microscopy for 3D and what the kind of sample is that you're looking at.

Q So there are situations where you want to use widefield imaging for 3D?

MR. HOLMAN: Objection. Form.

A There exists some situations where you could use widefield imaging for 3D.

Q And what are those situations?

A Well, for example, if you had, like, a single bright dye molecule labeling the target, in

that case, in principle, you could use widefield microscopy for assessing some 3D information.

Q And this was a situation we talked about earlier, where it's one single molecule, only one molecule, right?

A Well, what I would say is that, in that situation, in one single molecule, one could use widefield microscopy for assessing 3D, although, it certainly might not be the best choice for assessing 3D.

Q Would it be an unreasonable thing to do, to try to replace widefield imaging for 3D? Would that be unreasonable?

A Well, unreasonable is an odd word. But it would be -- the person would have known that, in some cases, you could use a different kind of microscope for getting better 3D information. The problem is that, again, it comes down to the sample question. So it's very hard to make general statements about whether it should be appropriate without knowing more of the details of what exactly we're talking about.

Q So you would not -- you would not state that, in general, widefield imaging is a poor choice for 3D? You wouldn't go that far, right?

MR. HOLMAN: Objection. Form.

A Well, I think, you know, it depends on, generally, what kind of samples we're talking about. So it depends, also, on what kind of 3D information I like -- I would like to obtain, which, in turn, depends on what kind of sample we're discussing.

Q Now, does the '554 patent, in your review -- let me strike that. Let me ask the question differently.

In your review, do you recall the disclosure in the '554 patent of improvements to widefield microscopy to make it more suitable for 3D?

A Can you say the question again, please.

Q In your review, do you recall any disclosure in the '554 patent of improvements to widefield microscopy to make it more suitable for 3D?

A Yes, I do. So one example would be column 8, lines 30 to 45, where the patents, the '554 patent discusses Sara Abrahamsson's work on fast multicolor 3D imaging using aberration-corrected multi-focus microscopy.

That would be one example that fits your question, sir.

Q Okay. And that was -- that's prior art, correct?

A That's prior art vis- -vis the '554 patent.

Q Anything else? Any other disclosure in the '554 patent of improvements to widefield microscopy to make it suitable for 3D?

MR. HOLMAN: Objection. Form.

A In the preceding paragraph, column 8, lines 15 to 30, there's prior art that discusses 3D deconvolution microscopy.

Q Anything else?

A Just to clarify, again, we're talking about specifically widefield microscopy, yeah?

Q Yes.

A There's column 7, lines 28 through 40, which describes the technique called light field microscopy. So I'd like to also mention that both the light field microscope and -- sorry, Sara Abrahamsson's fast multicolor 3D microscope are geared towards improving the speed at which you can acquire a photo stack. So they don't have -- they don't address the signal density issue that I raised, for example, or the resolution point that I raised in my declaration.

Q Okay. But that's prior art in here?

A The light field microscope is prior art, yeah.

Q Okay. Anything else? Any other disclosure in the '554 patent of improvements to widefield microscopy to make it suitable for 3D imaging?

A Just to clarify, the improvements that I discussed, you know, are they make it faster, but I wouldn't go so far as to say that make it suitable for 3D imaging.

Q So you're changing your testimony?

MR. HOLMAN: Objection. Form.

Q Because that was my question.

A Just to be clear, your question is, is there prior art in the '554 patent that makes the -- that would improve upon widefield microscopy?

Q No, that wasn't my question.

A Please repeat your question.

Q Is there any disclosure in the '554 patent of improvements to widefield microscopy to make it suitable for 3D?

A Okay. So thanks for repeating your question. I mean, the -- there's an assumption in your question, which is that -- which is that widefield microscopy is not suitable for 3D. So maybe you can clarify a little bit more what you mean.

Do you mean more suitable for 3D?

Q Sure, let's do it that way. Is there any disclosure in the '554 patent of improvements to widefield microscopy to make it more suitable for 3D?

A What do you mean by "more suitable for 3D," sir?
Q Better suited.
A In what sense?
Q Any sense. Any sense, whatsoever, in the broadest meaning of the term.
A Okay. Great. So, as I said, the Broxton light field microscope and the Abrahamsson fast multicolor 3D imaging disclosure, they both are geared towards improving the speed of widefield microscopy.
Q Okay. That's prior art.
Anything else?
A As I said before, the deconvolution reference, the '554 patent says because optical microscopy text points recognizes a point spread function, deconvolution methods reassign and focus light, which can serve to, effectively, increase resolution. So I'm just reading the method.
So this gets back to our earlier discussion about how, in principle, deconvolution can get you to the diffraction.

Q So the Broxton, Wilson, and Abrahamsson articles, that you mentioned in your previous answers, those are all prior art references?

A These are all prior art references.

Q Okay. Anything else in the patent that constitutes disclosure of improvements to widefield microscopy to make it better suited for 3D?

MR. HOLMAN: Objection. Form.

A Not that I'm aware of at this time.

Q Okay. Is there any disclosure in the '554 patent, that you're aware of, of improvements to light sheet microscopy to make it better suited for 3D?

MR. HOLMAN: Objection. Form.

A Not that I'm aware of, sir, no.

Q Do you know if the '554 patent contemplates widefield microscopy for use with the invention?

MR. HOLMAN: Objection. Form.

A My answer there is that the '554 patent makes many statements, like, according to one

aspect, this, according to one aspect, that. So the prior art disclosures that we just discussed fall under that umbrella.

So my understanding is that they are accounted for in the scope of the '554 patent by that language.

Q Is it your understanding, then, that the '554 patent contemplates that widefield microscopy (indiscernible) invention?

A All I can say, sir, is what I just said, which is that this language is used according to one aspect. You're the lawyer, not me. So I couldn't say that, explicitly, it calls out widefield microscopy.

Q You don't know if the '554 patent explicitly called out widefield microscopy for each of the inventions?

MR. HOLMAN: Objection. Form.

A I think my answer is the same as what I just said, sir. I don't recall seeing a place that explicitly details widefield microscopy in the '554 patent.

Q Okay. And does that surprise you?
A I really don't have much of an opinion about whether it surprises me or not. I never thought about it in that way, sir. I'd have to think about that a lot more. You're asking whether or not I find it surprising.
Q Would you have included widefield microscopy if you were the drafter of this patent?
MR. HOLMAN: Objection. Relevance. Form.
A I don't have an opinion about -- I'd have to mull over that carefully. My analysis here was, as described in the declaration, geared towards showing that Dr. Czymmek was incorrect in his assessment that one could simply combine the three references, Shen, Chen, and Cai, in order to arrive at the claims in the '554 patent. Didn't include speculation on whether or not the '554 patent would or would not include various techniques of 3D imaging in widefield microscopy.
Q Take a look at claim 69 of the '554 patent.

Do you see that reference to widefield microscopy?

A Uh-huh.

Q Any explanation for why they specifically claimed widefield microscopy?

MR. HOLMAN: Objection. Form.

A Sir, I don't have any detailed knowledge as to why the authors of the '554 patent, in dependent claim 69, refer to widefield microscopy.

Q Sitting here now, as 10x's expert on obviousness, do you have any explanation for why widefield microscopy is the only specific microscope microscopy modality that's claimed?

MR. HOLMAN: Objection. Relevance. Form.

A I don't have any special insight into what the authors of '554 patent were thinking in this particular claim. Of course, I should remark that this particular claim, by itself, is meaningless without the more global context of the independent claim 36. So, for me to read

widefield microscopy in isolation, again, it's just speculation. I don't have any deep feelings about this at this time.

Q I wasn't asking you to read it in isolation. I would never ask you to do that. Obviously you've got to read it in the context of claim 36.

Reading it in the context of claim 36, do you have any explanation as to why widefield microscopy was the only one that was specifically claimed?

MR. HOLMAN: Objection to form. Relevance.

A I don't have any special insight into that, sir, no.

Q Are you -- so you understand the way Dr. Czymmek presents his obviousness theories he relies upon Chen as his primary reference?

A What I understand about Dr. Czymmek's argument is that he attempts to bring in Shen and Cai, in getting to 3D MERFISH from Chen.

Q Would you be comfortable characterizing

Chen as the primary reference?

A I'd have to understand what exactly you mean by "primary reference."

Q It's his main reference, right?

A Certainly, Czymmek relies on Chen and brings other references to Chen.

Q You understand that for something to be obvious, if you're going to make an obviousness argument based on combinations of references, you have to be able to bodily incorporate the features from the second reference into the first.

You understand that, right?

MR. HOLMAN: Objection. Form. Foundation.

A I'm not sure exactly what you mean by "bodily incorporate," but what I can say is that Dr. Czymmek never elaborates on how to bring Cai into Chen, that's for sure.

Q You understand that you have to be able to take the two references and you have to be able to combine them without any modification, right? You understand that, right?

MR. HOLMAN: Objection to form.

A What I understand, sir, as I say in my declaration, in page 96, a POSA would have had no reasonable expectation of successfully modifying Chen's system to -- Chen's setup to arrive at claimed system.

And furthermore, I also assert, in my declaration, that Dr. Czymmek never indicates exactly how to incorporate these different references together.

What I mean by that is on page 94, perhaps you're saying the same thing here, Dr. Czymmek does not explain what specific modifications a POSA would have made to Chen's setup to arrive at the claimed system.

Q I wasn't asking that. I was just asking something more general about your understanding of what's required for obviousness.

Now, is it your understanding that for obviousness to exist based on two references, you have to be able to bodily incorporate the references from the first reference into the

second reference?

MR. HOLMAN: Objection. Form. Foundation.

A Again, I'm just going to repeat my statement. Like, what I understand is that in order for Dr. Czymmek's assertion to hold, there would have had to have been a reasonable -- there would have to have been a reason in which one would combine these references, and it would have to have been reasonably certain that there was success in so combining the references.

And then I'd also like to point out, again, that Dr. Czymmek doesn't explain how one could have modified his primary reference, Chen, in order to arrive at the system in claim 36. That's what I understand.

Q Now, with widefield imaging, is that ever used with this concept of making Z stacks?

A Widefield imaging can be used in the context of taking a Z stack.

Q Okay.

A Of course that's not what was done in

Chen, in the context of trying to get 3D information. But in general, one could use widefield microscopy in the content of a Z stack.

Q Okay. We'll come back to that in a little bit.

With regard to claim 36 of the '554 patent, you agree that claim 36 has no requirement as to a minimum number of nucleic acid molecules that needs to be analyzed?

A Can you repeat the question, please?

Q You agree that claim 36 has no requirement as to the minimum number of nucleic acid molecules that need to be analyzed?

A Well, what I can tell you is that claim 36 uses the following language: "Determining three-dimensional positional information of said one or more nucleic acid molecules," in part E of the claim, which should be understood as part of the whole claim.

Q Okay. So, you agree that there's a minimum number of nucleic acid molecules to be analyzed in claim 36, right?

A I agree with what I just said. That claim 36 recites determining three-dimensional positional information in one or more nucleic acid molecules.

Q Is there any requirement -- let me ask this question -- strike that.

What is the minimum number of molecules encompassed by the scope of claim 36?

MR. HOLMAN: Objection. Form.

A Well, this particular phrase says determining three-dimensional positional information of said one or more nucleic acid molecules.

Q So you can satisfy the claims through the analysis of only single molecule, correct?

A Provided all the elements of the claim are met.

Q There's no requirement that you have to analyze, for instance, a minimum of two molecules, right, one's good enough, right?

MR. HOLMAN: Objection. Form.

A I agree with the -- with what you're

saying, although I'd like to also point out that this is not the subject of my declaration, which I point out that one cannot get to this claim from Dr. Czymmek's argument, namely, combining 2D MERFISH Chen with Shen and Cai.

Q That wasn't a response. Remember we agreed upon you're going to be as direct as possible. You're going to get a full opportunity to restate your theory.

Do you understand that? They're going to do a redirect and you can say whatever you want.

Do you understand that?

A Well, I understand that that may happen, yes.

Q Okay. There's no requirement in the claims that the system has to meet a certain minimum resolution, right?

MR. HOLMAN: Objection. Form.

A There's no explicit reference to resolution in claim 36. Although a POSA would have understood the resolution would come to bear

determining three-dimensional positional information.

Q There's no minimum performance characteristic for the resolution, right?

MR. HOLMAN: Objection. Form.

A Again, if you're asking me does the patent recite a number, there's no number, but determining three-dimensional positional information requires an assessment of the resolution.

If that -- that's an important factor that comes into play in evaluating this claim, as I detailed in my declaration.

Q What is the minimum resolution requirement to satisfy the claims?

A Sir, it's contingent on exactly the system we're talking about, in the sample we're talking about. Depends on things like the NA, wavelength, number of molecules. So I can't give you a specific number in either.

Q You agree that the claim has to satisfy a certain resolution requirement, right?

MR. HOLMAN: Objection to form.

A The claim nowhere says anything about a minimum resolution number. That language is not in the claim. And, yet, as I've explained in my declaration, resolution is an important factor in determining three-dimensional positional information.

Q Now, is there any requirement in the claim that precludes the use of overnight hybridization in preparing your sample?

A Are you talking about claim 36, sir?

Q Any of the claims.

A I don't recall any language about overnight hybridization in any of the claims.

Q Is there any requirement in the claim that mandates a streamlined workflow?

A I don't recall, again, seeing any language with those words in the claim. But one thing I will say is that, again, as I kind of explained, in order for this to be successful, all of these different claim elements must work together.

Q You agree that if there's a system that's in the prior art, then it has a tedious workflow, that means it wouldn't satisfy the claims of the '554 patent, right?

MR. HOLMAN: Objection. Form. Foundation.

A I don't have an opinion about tedious workflow being limiting or not. I haven't thought about it.

Q Do you see any requirements in the claim that preclude the use of tedious workflow?

A I don't see any requirements that preclude tedious workflow.

Q Are there any claim requirements that require that the system be compact and not sprawling?

A There are no requirements like that. But as I said earlier, in my testimony, having a compact monolithic system helps vis- -vis objective indicia, as I mentioned, and having a system that is sprawling makes it that much more difficult to modify for some particular task.

So, for example, Chen system is one that I characterized as not compact and sprawling in my declaration and it doesn't satisfy this claim.

Q You said that having a compact monolithic system helps vis- -vis objective indicia.

What do you mean by that?

A What I mean by that is that in my declaration, when I go through the features of the Xenium and CosMx system that embody the claim, part of the reason that the systems are successful is the fact that they're compact and monolithic.

And this is also why they receive the praise they did, which I understand can be evidence that the invention is not obvious.

Q And we talked about this earlier, there's no requirement in the claims for the system to be compact and monolithic, right?

MR. HOLMAN: Objection. Form.

A The claims don't exclude that, that possibility, they include it. And I don't have an

opinion on whether or not they restrict the claims in any way.

Q Okay. Do the claims require any minimum sample thickness?

A I don't recall seeing any statement about minimal sample thickness. Although, as we discussed, and as is in my declaration, the sample thickness certainly has a bearing on the ability to determine accurate three-dimensional positional information, particularly --

Q The claim --

A -- in the context of MERFISH, in which there are many nucleic acid molecules that are stained.

Q So, the claim doesn't have any requirements with regard to the sample type, right?

A Well, the claim specifies nucleic acid molecules. So that sample type is explicitly in the claim.

Q Okay. Other than the fact that you're analyzing nucleic acid molecules, there's no

limitation on the sample type, right?

A There are limitations in the sense that a sample type, presumably, must fit into the sample holder -- the sample must have a volume and so on and so forth. So there are -- there are implications on the sample on the basis of the writing in the first few claim elements.

Q We talked about this a little bit earlier. A single cell, that has a volume, right?

A A single cell has a volume, although, of course, the single cell can have a volume and one can image it only in 2D, as in the MERFISH paper by Chen.

Q But you could also image a single cell in the 3D paper, by virtue of the fact it has a volume, right?

A Well, your success for that imaging will depend on what exactly is labeled in the sample. As we discussed, Chen does not report any 3D in their sample.

And that's very likely, in part, because of the nature of that sample. So you can

image a cell in 3D, but it doesn't mean that you'll be successful in imaging the cell in 3D.

Q And it was known in 2015 that you could image the cell in 3D, right?

MR. HOLMAN: Objection. Form.

A In 2015, it was known that there were some cells that could be imaged in 3D.

Q We talked about this earlier, the imaging of single cell in 3D, that's within the scope of the claims, right?

MR. HOLMAN: Objection. Form.

A The claim does not -- there's no language in the claim about cell -- about a cell having -- there's no language in the claim that restricts what you just said.

Q That precludes the analysis of the single cell, right? There's no language in the claim that precludes the analysis of a single cell, right?

MR. HOLMAN: Objection. Form.

A As far as I can tell, there's no language in this claim that precludes that.

Q Okay.

A Unless we're talking about determining three-dimensional positional information of said one or more nucleic acid molecules that the sample type is as of MERFISH. In that case, as I described in the declaration, one couldn't get to the three-dimensional positional information of said one or more nucleic acid molecules simply by combining Shen, Chen, and Cai, as Dr. Czymmek outlines. So that would be my exception to what I just said.

Q Sorry, what's the exception? I couldn't understand that at all.

A Yes. In my declaration, I make the point that you cannot get to claim 36, as Dr. Czymmek suggests, by combining Chen, Shen, and Cai.

Q Okay. So all you're doing is reiterating your argument that you don't think Chen, Shen, and Cai renders claim 36 obvious? That's it?

MR. HOLMAN: Objection. Form.

A I am reminding the record of that point, yes.

Q Okay. Is there any requirement in the claims that imposes the capability of working well with high densities of targets?

MR. HOLMAN: Objection. Form.

A There's no requirement of that in the claim. Although, as I discuss in my declaration, implicity, there's the point that in order to determine the three-dimensional positional information of said one or more nucleic acid molecules, one would have to deal with the kinds of issues that a high density -- as a sample for high density.

Q Now, the claims also don't require that that sample be live, right, they can be dead?

A I don't recall any language about live or dead in the claims, sir.

Q All right. Let's go to the next exhibit here.

(10x Genomics Exhibit 2078 previously marked for identification and retained by

counsel.)

Q Okay. I've handed you Exhibit 2078.

Do you recognize this document?

A Yes, I do.

Q All right. Let's go to Section 4.1. This is a section entitled "Three-Dimensional Optical Sectioning." This is describing, in this section, how a person of ordinary skill in the art would generate a 3D image from a series of 2D images; is that right?

MR. HOLMAN: Objection. Form.

A Yeah, lines -- let's see, can be used to collect a series of 2D images in a specimen by moving the focal plane across the 3D specimen. That is what it's saying here, sir.

Q And that's on page 24, correct?

A Those sentences are on page 24.

Q Okay. So let's take a look at Figure 17.

Figure 17 is showing those series of focal planes?

A Yes.

Q Okay. And each of those focal planes is a 2D image?

A Each of those focal planes, it refers to a 2D location, 2D plane.

Q And can you tile those adjacent focal points to make a 3D image?

A In principle, you can tile those focal planes to make a 3D image. Of course, that's not what was done in the reference, the prior reference image that was suggested by Dr. Czymmek.

Q Now, can you also tile adjacent areas to put together a bigger 3D image, so you can tile the focal planes and can you also tile adjacent areas to make it even thicker?

MR. HOLMAN: Objection. Form.

A When you say "adjacent areas," do you mean X, Y, Z?

Q Yes. So let's define the different focal plane as the Z-axis. With that definition, the adjacent areas, I would say, is different positions on the XY-axis, the XY direction, the XY plane.

Can you tile together the different images in the XY, along with the images in the Z direction, tile all of those together to make a bigger 3D image?

MR. HOLMAN: Objection. Form.

A I mean, in principle, you can do that tile. I think depending on exactly what you mean by "tile," you need, of course, the appropriate tools to do that tile.

Q By "tools," you mean software tools?

A Software tools.

Q And when were those software tools available? Were they known to the person of ordinary skill in the art in November of 2015?

A I suspect they were known to a POSA in 2015.

Q And we talked about this earlier, the strategy of tiling adjacent focal planes to generate a 3D image, that was known in November of 2015, right?

MR. HOLMAN: Objection. Form.

A I think tiling was known in 2015. And,

again, I'd like to reiterate that, of course, this method was not applied to do any 3D analysis in Chen 2015.

Q Now, this tiling method, where you tile the adjacent areas and the adjacent focal points, is that something that can be done using widefield microscopy?

A Well, the success of that procedure will depend on how much out-of-focus light there is in the sample, sir.

Q But it could be done depending on the sample type, correct?

A Depending on the sample type, it could be done.

There's no evidence, of course, that this could be done in 2D MERFISH upon which Dr. Czymmek's opinion applies.

Q Okay.

MR. WALTER: Do you mind if we take a break?

MR. HOLMAN: Sure.

(Recess taken from 2:16 p.m. to

2:32 p.m.)

(Exhibit 1074 marked for identification and attached to the transcript.)

BY MR. WALTER:

Q Dr. Shroff, I've handed you a document that's marked as Exhibit 1074. It's a publication entitled mRNA quantification using single-molecule FISH for Drosophila embryos.

Do you recognize this document?

A I would like to point out, for the record, that this is not in the list of documents that I specifically reviewed for my declaration. But of course I am familiar with this document because I'm the author of the document.

Q Now, this was published online on June 8th, 2017.

Do you recall when you were doing the work that led to this publication?

A I do recall.

Q When did you do it?

A Around 2015.

Q But was it throughout the year of 2015?

A I can't remember exactly. You know, I cannot recall the exact time period, but it would have been a couple of years before the publication date, 2017.

Q Why do you say it would have been a couple years before it? Was this one slow to get published or something?

A In general, it takes, you know, research can be anywhere from a few years to several years, or even more, before the thing comes out in print.

Q Do you remember when you submitted this one? I'm having a tough time finding the submission date?

A I really can't remember, sir.

Q All right. In general, do you know what the subject matter of this publication is?

A In general, I do know what the subject matter of this publication is, yes.

Q What was this paper about?

A I think it was about using a super-resolution technique that I invented to do

single-molecule FISH of a few numbers RNA in the Drosophila embryo.

Q So this was a single-molecule analysis using FISH?

A Yes, it was, sir, as described in the abstract.

Q And how many molecules were you looking at?

A In terms of absolute numbers of molecules, I really can't remember. In terms of types of molecules, far fewer than MERFISH. That, I can remember.

Q Do you remember a rough order of magnitude as to how many molecules we're looking at?

A Just to make sure I understand the question. Are you talking about the total number of RNA molecules or are you talking about the number of types of different RNA molecules?

Q The number of types.

A Again, it's been a while since I've looked at this explicitly. But I see from

Figure 2, the caption, that there were 32 single-molecule FISH probes on one kind of RNA, but then this figure describes four types of RNA.

So, again, going just from my recollection, I would have to say, you know, less than ten types of RNA. And I don't know the numbers of molecules involved.

Q And what was the microscopy modality that you used for this work?

A Well, the sort of star of the show here was the microscope that I invented called ESEM. But this paper is not restricted to ESEM.

Q And that was a super-resolution imaging approach?

A That's correct.

Q And when did you invent ESEM?

A Well, ESEM is cited in the '554 patent. The paper came out in 2015, me describing ESEM. As far as the patent invention date, we'd have to consult the literature. I don't recall.

Q Now, you state in the abstract, second-to-last sentence, "With minimum guidance, a

graduate student can successfully implement this protocol."

Do you see that?

A I do see that writing, yes.

Q Okay. What did you mean by that?

MR. HOLMAN: Objection. Relevance.

A Well, this paper is a protocol published in the protocols journal and it's written in such a way that a graduate student could, with minimal guidance, go through all the steps of the protocol and follow them. That's what I mean by that.

Q And that includes using the ESEM microscopy method?

A So refreshing my memory as to ESEM used in this. Because one of the ISIMs that was developed was of the same nature as the Chen MERFISH microscope, namely a sprawling system that would have been laboriously used by others.

But then there was also a commercial ESEM which was later invented with the expressed goal of a smoother workflow integration.

And so, I am just trying to remind myself as to which one was used in this paper.

Again, this has been -- this is not a paper I reviewed, so I don't have all the answers at hand.

Okay. Something to say about that is that this paper assumes that the user would have sent ESEM around in their lab. So it would be read in that context.

Q So using that ESEM, which you had published in 2013, you were able to do 3D imaging on single molecules and the number of targets you said was, what, about 30?

A This shows the number was less than 30. But, so, it's very different than the scope of the patents that we were discussing today. Yeah, like, not in the MERFISH category at all. So that's a more important point of distinction. I'm just trying to get a sense as to exactly how many.

So, in Figure 2, there are four mRNAs, mRNA types. And Figure 5, there are five mRNA types.

So as I point out in the declaration, MERFISH is a different sport than what I describe in this paper.

Q By "different sport," you mean MERFISH was doing larger numbers of targets?

A Larger number of targets. But also, for the reasons that I described in my declaration, more difficult imaging problem because of the number of criteria, as we discussed. Resolution, background, how to focus light, all of these -- all of these problems compound in the limit of massively multiplexed FISH, for which this technique is not.

Q Okay. But this technique, this was multiple targets, there was single -- sorry, this technique, that's in Exhibit 1074, your publication on the Drosophila embryos, that was single-molecule analysis, it was multiple targets, and it was 3D imaging, right?

MR. HOLMAN: Objection. Form. Relevance.

A Yeah, I'm not sure how relevant this is

because in --

Q Just answer the question.

A I am answering the question. Unlike the MERFISH paper, this is a handful of targets. You know, it's possible the sample is something that was clear. I would have to review my own knowledge of the paper, which has been a hot minute. It's not an apples-to-apples comparison, I guess is my point.

Q I just want you to confirm. This publication, Exhibit 1074, single molecule, multiple targets, multiple nucleic acid targets, and it was 3D, correct?

MR. HOLMAN: Objection. Form. Relevance.

A It's a Drosophila embryo with a handful of RNAs. And the paper was published after the 2015 paper. So there are important differences between the Chen, as we were discussing, and Czymmek's opinion. I would says it's, like, your apples and oranges.

Q Okay. Now, the Drosophila embryo

sample, how thick were those samples?

A I can't remember. I honestly can't remember how thick they were. I can't give you a number.

Q Are you able to identify how thick the sample are by taking a quick look at your publication?

MR. HOLMAN: While the witness reviews the publication, I would like to generally object under FRE-001 and 003.

A I would like to make a point that in Figure 2A, there's a Drosophila embryo and a scale bar of Figure 2A is 10 micron -- is 5 microns in the center and 10 microns on the outside. So that gives some sense as to the overall scale of the Drosophila embryo.

But I think it's also important to point out that we didn't image through the entire Drosophila embryo, rather, we imaged, you know, some fraction of those planes.

So it's not the case that simply because the overall sample is much larger than a

single cell, it was successfully imaged that entire sample with the microscope. That's an important detail that I'd like stated for the record.

Q All right. And you said you were doing this work for, roughly, a couple years before the publication in June of 2017?

A Very roughly. And, again, my answer is not exact because I simply don't remember, having not seen this paper in almost a decade.

Yeah, just one point that I'd like to make, since you brought this paper up, and the first place is under limitations. This paper states when quantifying uniformly dispersed unlocalized mRNAs, our method performs exceptionally well unless the abundance of transcript exceeds the concentration in which the individual transcripts are no longer discernible as a fraction of response.

And this is exactly the kind of signal density problem that I described in the declaration, albeit a very different sample.

So it goes to show that even in a very different sample, the concern about signal density is limited in the sense that there's no guarantee one can image mRNAs in a sample like this unless they're sparse. In this case, almost only a handful.

Q Take a look at the right-hand column of the first page, the introduction.

A Right-hand column, first page.

Q You state that after the imaging, the 3D images are deep involved and single mRNAs are detected and counted using a freely available spot-detection algorithm localized, which was developed in the MATLAB programming language.

Do you see that?

A I do see that. And the relevance of that to the discussion of Czymmek is not clear.

Q That Airlocalized software, that was available well before November 2015?

A If I look at citation 9, I see that that paper was published in 2011. But that, of course, by itself doesn't prove anything. There

are many software packages that were available before the Czymmek -- before the 2015 MERFISH paper.

Q Those were publications for de-convoluting light microscopy image data to detect individual molecules?

MR. HOLMAN: Objection. Form. Foundation.

A I have no idea if those papers are what you just said. I'm just pointing out that there were many method papers that were involved before the 2015 paper. So my point is that merely because the paper was available before 2015 doesn't prove anything vis- -vis the validity of that paper for methods in MERFISH.

Q Okay. Here, you cite a paper from 2011 that you were using, your laboratory was sought for the development in MATLAB and that was for de-convolving microscopy data to detect individual mRNA molecules.

Was there other software that would perform similar functions that was similarly

available to the people skilled in the art prior to November 2015?

MR. HOLMAN: Objection. Form.

A I can't say definitively there was other software. There may be, there may not be. I couldn't, for example, give you the names of any software that, like this name, we're using in context. Again, I would like to say, for the record, just because the software exists and was used in this particular instance, after the 2015 paper, does not -- it does not follow that this offer couldn't be used in the context of MERFISH, as noted by Czymmek.

Q Do you know, one way or the other, whether it could be used in the context of MERFISH?

MR. HOLMAN: Objection. Form.

A Unless we did the experiment, I can't definitively say, one way or another, if this software could have been used on that data. All I can say for sure is that the nature of this data is much cleaner than the kind of massive multiplex

data in the Chen paper. That much is clear from the figures of this paper.

(Exhibit 1075 marked for identification and attached to the transcript.)

Q All right. I've marked as Exhibit 1075 a publication entitled "Confined Activation and Subdiffractive localization Enables Whole-Cell PALM with Genetically Expressed Probes."

This was published in 2011.

Are you familiar with this publication, Dr. Shroff?

A Just like the MERFISH paper, this is a paper I'm the author on, I authored this paper, so I do remember this paper. Just like the other paper, I have not reviewed this with an eye to what we've been discussing throughout the day, namely, the Czymmek declaration, my refutation of the Czymmek declaration, and the relevance of this paper for discussion is unclear.

Nor can I be expected, in the time we have remaining, to render an accurate opinion of this paper. It's been more than decade since I've

looked at it.

Q This publication was 3D imaging, correct?

A This paper, just as the abstract describes, describes a method for improving the state of the art at that time for 3D PALM imaging. It is not a general paper that describes the method that will be generally applicable to improving 3D microscopy.

Q Do you remember how thick your samples were in this sample, in this publication?

MR. HOLMAN: Objection. Form. Relevance.

A I'm looking at the abstracts and I see that the sample was 8 microns, which is about the thickness of a single cell.

Q These were samples at volumes?

A These samples had volume.

Q Were you looking at nucleic acids in this claim publication?

MR. HOLMAN: Objection. Relevancy.

A No nucleic acids in this reference.

Q Could that iPALM -- excuse me. Could this PALM method, that's described in this publication, be used for nucleic acid molecules?

A Well, we didn't show that in this paper and, so, I'm unwilling to speculate if it could be used. I mean, it certainly could have been done. I don't know. The short answer is I don't know.

Q Now, if you go to page 2 on the right-hand side. It states "Conventional temporal focusing microscopy confines two-proton illumination to a single plane," and then it goes on.

Do you see that?

A Sorry, where are you looking? Page 2 -- yeah, can you --

Q Page 2.

A Yes.

Q Right-hand column.

A I see those words, yes.

Q Okay. What is conventional temporal focusing microscopy?

A Temporal focusing microscopy is a

technique invented by an Israeli group that uses an ultrafast pulse to illuminate a specimen. And it achieves a two-photon-like effect. Yeah, I mean, I could go into more details, if you want me to. I don't know if you need me to.

Q That was a method as of 2011, when you wrote about it in that publication?

A It was a niche method. The reason I'm calling it conventional here is that I contrast that method, in this paper, to another method whereby I scan the pulse using a gavel. So the, you know, the word "conventional" is misleading here. A person would have understood conventional method to be something like a light sheet microscope or a spinning disc microscope at the time of the 2015 '554 patent.

The subset of people that knew what the heck a temporal focusing microscope is is extremely small compared to -- these people are not POSAs, they would be considered experts. Experts in the art. And then, among those people they would have to read this paragraph for context

to understand what I mean by conventional temporal focusing.

Q Okay. This temporal focusing microscopy method, this was published when?

A Well, look at reference 19. 2005, sir.

Q So a decade before the priority date for the '554 patent?

A A decade before the '554 patent. And it almost certainly would have had nothing to do with the '554 patent.

Q Okay. This was a technique that would allow optical sectioning at depths of up to a hundred microns; is that right?

MR. HOLMAN: Objection. Scope.

A I'm not sure where you're getting the hundred microns, sir.

Q Okay. I'll read in the record. "Conventional temporal focusing microscopy confines two-photon illumination to a single plane by scanning an intense line focused across a sample in picosecond time scale, which allows optical sectioning at depths greater than a

hundred microns."

A Thank you for clarifying that.

Q Did I read that correctly?

A You did. That is what that sentence says.

Q Okay. Let's go on to the next document.

A Of course. In order to use this technique, one would have to have had a two-photon activator dye, would have had to have known how to put these elements together. And it's unclear to me that this method would work, at all, for any of the dyes used in the body of work we consider today.

So, while it's true to say, as you just read, that the conventional temporal focusing microscopy, in principle, can allow optical sectioning of depths greater than a hundred micron, it's unclear and probably not true that this would have applied in the context of the '554 patent at all.

And furthermore, optical sectioning, as

I detail in my declaration, is distinct from three-dimensional imaging. They're two separate concepts.

MR. WALTER: Okay. To the extent you folks try to rely on that, I'm going to have that stricken. There was no question pending and it wasn't called for by the question.

MR. HOLMAN: I would like to generally object to Exhibit 1075 for FRE-401 and 403.

(Exhibit 1076 marked for identification and attached to the transcript.)

Q All right. I've marked, as Exhibit 1076, a publication entitled "Influenza A Virus Assembly Intermediates Fuse in the Cytoplasm," published in March 2014.

Do you recognize Exhibit 1076, Dr. Shroff?

A Yes. Again, this is a paper that I co-authored. It's, again, a paper that has no relevance to our discussion, it's not in my bibliography, and the methods are unrelated to Dr. Czymmek, his erroneous declaration, my

declaration, but I do recognize the paper.

Again, it's been more than a decade since I've looked at this paper. So for me to render an accurate opinion on this paper is questionable at best.

Q Let's take a look at the author summary on page 2.

A Author summary on page 2, yes.

Q There, you explain that you did three-dimensional localization of four different viral RNA segments?

A Yes. That is what those words state.

Q So this was 3D imaging?

A This was 3D imaging of a handful of different proves, yes.

Q They were nucleic acid particles that you were visualizing?

A In this case, there were viral RNAs. So, yes, that falls into the rubric of nucleic acid.

Q What's being shown in Figure 2?

A All right. So I'm reading the caption

here. Figure 2 are -- is a 3D rendering of a cell that has been infected with viruses and it looks like what's being shown here are puncta corresponding to the probes. Different multicolor probes. And the DAPI stain used is the blue.

Q Puncta, is that, like, a German word?

A Puncta is just a word meaning small object, sir.

Q How do you spell that?

A P-U-N-C-T-A.

Q What kind of microscopy modality was used for the experiments in this publication?

A So, among the different microscopy techniques, Leica SP 5 white-light laser focal microscope would be one.

Q What kind of microscopy approach was that? Was that light speed, widefield? What would you characterize that as?

A Those are focal microscopes, sir. So I believe Figure 2, Figure 2 is a focal microscope. And then, in addition to that, there were proteins that were in Figure 6.

Q How thick was the sample in which you imaged the RNA nucleic acid molecules?
A I can't recall exactly what the sample was, sir.
Q Do you want to take a moment to review it and then you can let me know?
A So, for example, in Figure 2, there is a scale bar, scale bar is 4 microns and a whole-cell image. So, some number of microns. That's about right.
Q So was this 3D imaging of a single cell?
A This was --
MR. HOLMAN: Objection. Form.
A This was 3D imaging of a single cell with four distinct labels.
Q And why did you use four distinct labels?
A I can't remember. I honestly can't remember.
Q What would have happened if you used only one label?

A I mean, I think in this case, the investigator was primarily interested in where these foci were. And the foci were different kinds of foci. But I think this is without imaging four distinct vRNA segments. Again, I'm just reading what's in the caption here. It's been a while, I can't recall.

Q When you say "the investigator," that was you, right?

A Sir, I was involved in microscopy part of this work, but I'm not a virologist.

Q Okay. I understand.

A Again, I would like to, sir, just remind the record what we're seeing here is a multicolored 3D image of a cell, which is unsurprising because that part was known. But what's relevant for this discussion, again, is the ability to carry out three-dimensional localization of nucleic acids in a dense context, as explained by Dr. Czymmek in the MERFISH paper.

Again, what was done here is conceptually and practically quantitate from the

erroneous statement of Dr. Czymmek that one could combine Cai, Shen, to the MERFISH paper in order to get massively multiplexed 3D MERFISH data.

Q Now, when you said "dense context," what do you mean?

A What I mean is massive and multiplexed. So many, many, many kinds of mRNA in a single cell.

Q Now, there's nothing in any of the claims that requires what you just described as dense context, right?

A I'm really, again, taking apart Dr. Czymmek. And it's Dr. Czymmek who was discussing the 2015 paper, Chen, in the context of Shen and Cai. My context should be understood accordingly.

MR. HOLMAN: I would just like to generally object to Exhibit 1076, FRE-301 and 303.

(Exhibit 1077 marked for identification and attached to the transcript.)

Q All right. I've handed you a document that's been marked as Exhibit 1077. It's a

publication entitled "Image-based transcriptomics in thousands of single human cells at single-molecule resolution."

Do you recognize this article?

A No, I do not.

Q Never seen it before?

A I've never seen this paper before, at least in my recollection. This is not a paper that is part of my bibliography nor is it a paper that I'm familiar with.

Q You can tell from the abstract of this publication, it pertains to FISH?

A FISH is in the first three words, so, in that sense, I agree that it's about FISH. Once again, it looks like a paper that has no relevance to our discussion at all. Of course that's just based on my cursory examination because I've never seen this paper before.

Q And you agree this is a single-molecule paper?

MR. HOLMAN: Object to form. Relevance.

A The title says single molecule. In order to be absolutely sure, I would need to read this paper.

MR. HOLMAN: I generally object to 1077 under FRE-401 and 403.

A I would like to note, from my cursory examination of this paper, I do not see any 3D localization at all.

(Exhibit 1078 marked for identification and attached to the transcript.)

Q Okay. Now this is -- handing you Exhibit 1078. Let me finish asking this question of 1077.

If you look on Figure 1A, there's a reference to branched DNA technology.

Do you see that?

A Are we talking about the Battich and Pelkmans reference, sir?

Q Yes.

A So, Figure 1A.

I'm looking at Figure 1A. And what, again, would you like me to comment on?

Q Do you understand that figure to be depicting something called branched DNA technology?

Do you know what that is? Have you heard of that?

MR. HOLMAN: Objection. Scope.

A I've never heard of branched DNA technology.

Q What do you understand being depicted in Figure 1A?

MR. HOLMAN: Objection to relevance.

A Figure 1A looks like a bunch of blobs, which would be dyes, I'm not sure. Looks like those dyes are attached to something else, which looks like a purple rod, and that purple rod is attached to something else to what looks like, I assume, is a nucleotide because it says NT.

Q Okay. Let's take a look at Exhibit 1078. I'm showing you the supplementary information.

And let's go to supplementary Figure 7?

A Again, a document I've never seen

before.

Q And if you take a look at paragraph -- the captioned supplementary Figure 7, Section I, it says "comparison of 3D spot detection that is using 10 Z stacks and 2D spot detection."

Do you see that?

A Those words are on the page, sir, I see that.

Q You understand that's indicating that 3D imaging was done?

MR. HOLMAN: Objection. Scope. Relevance.

A I mean, I understand that it means that 3D spot detection was done. As for the 3D imaging, I would have to read this paper throughly to render an opinion of exactly what that means and how it relates to any of the material that we've been discussing today.

If I look at, you know, the images of this figure, it sure looks like 2D spots to me.

Q What does it mean to you when it refers to 3D spot detection in 10 Z stacks?

MR. HOLMAN: Objection. Scope, relevance.

A 3D spot detection and 10 Z stacks is also something that I don't know how to interpret.

What does it mean to have 10 Z stacks, for example? 3D spot detection. 3D spot detection can mean any number of things. Regardless, I don't see any localization in 3D, which is another point of difference. So, for example, the Chen paper, that detects molecules in more than one plane, as I can tell in my declaration, but it doesn't localize anything in 3D. Similarly, here, I have no idea if it's the same as in Chen or different. From this one isolated phrase, it's impossible for me to say what they're talking about.

Q Is there anything in the claims of the '554 patent that requires mobilization?

A Requires mobilization? I would have to check the '554 patent again.

MR. HOLMAN: While he's checking, generally object to Exhibit 1078 under FRE-401,

403, and 901.

(Exhibit 1079 marked for identification and attached to the transcript.)

A I don't recall seeing that phrase in the context of the '554 patent, sir.

Q Okay.

A 1079?

Q Yeah, 1079 is supplementary Table 5 to the paper we've been looking at.

A Okay.

Q There is a row that refers to microscope.

A Yes, I see that row, sir. Again, I would like to state that I've never seen this table before in my life.

Q Are you familiar with Visitron Systems?

A I'm not familiar with Visitron Systems.

Q How about the Yokogawa CellVoyager microscope? Is that something you're familiar with?

A I'm familiar with Yokogawa, but I'm not sure what the CellVoyager is.

Q And there's entries near the bottom that refer to Z step. What do you understand that to be referring to? (Indiscernible) just refer to Z step and acquired planes.

What do you understand those to be referring to?

MR. HOLMAN: Objection. Scope. Relevance. Foundation.

A I'm not a hundred percent sure what Z step means in this context because I've never seen this paper -- this table before in my life. But in an attempt to answer your question, Z step is typically the step between planes in a Z stack. Of course, I feel obligated to also point out that just because a Z stack was taken doesn't mean that molecules were localized in 3D.

A good example of this would be in Chen 2015, where there were some limited Z stacks taken to find if molecules existed inside the focal point or outside, but there were no axial localization.

So Z step, by itself, doesn't tell me

much, sir.

MR. HOLMAN: Generally object to Exhibit 1079 under FRE-401, 403, and 901.

Q Okay. Let's go to the Cai reference, Exhibit 1004.

A Cai reference.

Q 1004.

Okay. Let's go to column 46. Let's take a moment. I'm going to start with Figure 16.

What's being depicted in Figure 16?

Do you know?

A All right. So Figure 16, I'm reading the figure caption on column 11. Clarity with Nis 1, it's a 1 millimeter thick coronal section of a mouse brain that has been cleared with a stain that highlights neurons, NIS 1. And it looks like the labels there are NIS 1 and green QIFB. So that's according to the timeline that was depicted in Figure 16.

Q Now, if you look at the figure caption, it says "3D coronal rendering of the motor cortex."

What does that mean to you?

A It means that on this particular brain sample, somebody associated with Cai took a stack, using some microscope, and then they rendered that stack into the image that we see in Figure 16.

Q That that's tiling of focal planes approach that we talked about?

MR. HOLMAN: Objection to form.

A I couldn't say that for sure, sir. I don't know if this was tiled or not.

Q You agree that Figure 16 on the left is a 3D image?

A I mean, I agree that it's a rendering of a 3D object.

Q Lets take a look at column 46.

A Yeah. 46. Okay.

Q Why don't you review lines 49 on column 46 to column 47, line 12.

Let me know when you're done.

A Sorry. Column 46, and then lines 40 -- which lines did you want me to review?

Q Column 46, line 49.

A Line 49. Okay.
Q To column 47, line 12. So it's one paragraph.
A Okay. Gotcha. Okay.
Q Now, having reviewed that, do you have a better understanding of what was done in connection with Figure 16?
A Not really. I mean, most of this has to do with the sample preparation. I mean, like I said, it's a rendering of a 3D object. But maybe I missed it. I don't see anything in here, this paragraph, anything about tiling or anything else.
Q Okay. It's 3D data, correct?
A What's shown in Figure 16 is a rendering of some 3D data.
Q And that was data that was generated to light sheet microscopy with clarity?
A Yes.
Q What is clarity?
A Clarity is a clearing technique that is used to render a sample transparent and, ideally, of the same refractive evidence. I feel it's

important to state that that's a clearing method. But in order to successfully realize clarity, one would have to have imaged the clarity with the appropriate optics, including the right refractive index objective lens.

You know, as with any imaging technique, the choice of imaging parameters determines the image that we see. And so, it's clear, from the scale of this figure, that half the context of this figure, this is nothing like, for example, the kind of data in the 2015 MERFISH paper of Chen.

Q Now, let's go to Figure 18.

A Yes, Figure 18.

Q What is being shown in Figure 18?

A Again, looking at the caption in Figure 11 -- in column 11 of this document, what's rendered here appears to be beta actin mRNA in a 3D reconstruction, where the beta mRNA has been amplified by a technique called HCR.

Q So this is 3D data in Figure 18?

A It's a rendering of 3D data, sir, yes.

Q And this was done using spin microscopy method?
A It was done with a spin microscope.
Q And it's nucleic acid molecules, correct?
A Single beta actin mRNA.
Q And they went over a hundred microns?
A Unclear -- yes, I see that the caption says the slice was scanned over a hundred microns.
Q Now, what, again, was HCR?
A HCR stands for hybridization chain reaction, and it's another method whereby one can amplify signal from nucleic acid.
Q And what was the benefit of that approach for microscopy methods?
MR. HOLMAN: Objection to form.
A I'm going to have to review some material on this in my declaration. It will take me a moment to find it.
So in paragraph 95 of my declaration, I discuss what HCR is. And it's an amplification technique used to effectively image the signal of

the background.

And I also say, which I stand by, a POSA would have understood that this is an attempt to mitigate the low-resolution imaging optics used in this technique for the application of single-data mRNA.

Q Have you ever heard of a LSM510 microscope? LSM510 META?

A I've heard of the L510 META.

Q Was that a microscope that could be used for previews?

A I think I need the specifications to be sure about that point. But I believe so. From my memory.

Q Okay. When was that microscope available?

A I don't know.

Q Was it before 2015?

A I don't know.

Q Now, is Cai disclosing single-molecule detection?

A Do you mean --

MR. HOLMAN: Objection. Form.

A Do you mean in the context of Figure 18 or...

Q Yeah, let's start with that.

A I'm not sure, sir.

Q Okay. Was that because of the use of HCR?

A That's because I'm not sure that I see any single molecules in these images.

Q Now, have you heard of software called 3D STORM?

A I've not heard of software called 3D STORM, but I'm aware that there's a technique called 3D STORM.

Q Okay. And how long has that been available for?

A I believe the first 3D STORM paper was published in 2008.

Q And what is it used for?

A Like we discussed earlier, STORM is one of the super-resolution microscopy methods that, in some cases, can be used to alleviate problems

of signal density.

Q Can it be used for individual nucleic acid molecules?

A Well, I think I'd have to see an example of that in action to answer your question. I know that it is -- was around the time of 2015 paper that had been published. But as far as your specific question about nucleic acids, I don't know the answer to that.

Q All right. Let's go to paragraph 104 of your declaration.

Now, in paragraph 104 of your declaration, you are looking at later work from the group that developed MERFISH. And you contend that that later work is relevant to whether a person of ordinary skill in the art would be motivated to modify the Chen paper to arrive at 3D MERFISH; is that fair?

MR. HOLMAN: Objection. Form.

A Yeah, I'm just reviewing what I wrote here. So, there's a sentence, this motivation to increase the multiplexing of 2D MERFISH -- 3D

MERFISH is reflected in later work from the same research group, and then I go on to describe innovations in MERFISH conducted by the same group whereby they could do more, more, meaning more throughput.

So I think it's fair to say that I'm using this as an example, that even the same group went in the direction of potential throughput rather than 3D, as described in this later paper, as you say, published in -- well, let me check the publication date, I believe 2016. 2016.

Q All right. Let me.

A Let me also point out that this is, of course, the same group that performed 3D STORM. And so, the same group, as I'm saying in this declaration, went to the direction of higher throughput.

(10x Genomics Exhibit 2009 previously marked for identification and retained by counsel.)

Q I'm handing you Exhibit 2009.

Do you recognize this publication?

A This publication is not in my bibliography, but I have seen this publication before. So I recognize it, although I'd have to say I'm not familiar with it in the same way that I am with the other literature in my declaration.

Q I'm surprised it's not in your bibliography.

A I would note the date on this publication is 2020, well after the 2015 publication.

Q This is a publication on 3D imaging, correct?

A Has that name in the title, sir. 3D organization of chromatin.

Q And this is a publication based on MERFISH?

MR. HOLMAN: Objection. Scope.

A In the abstract, it says next to report MERFISH-based method for genome scale chromatin tracing.

So, I'd have to agree that this paper, again, published well after the art that we've

been discussing today, is based on MERFISH.

Q Okay. So you don't dispute that the group that published Chen, they did extend MERFISH to 3D?

A Sure. Eventually, they extended it.

Q Do you know if they did or didn't? They did, right? You know that?

MR. HOLMAN: Objection. Form.

A I mean, in 2020, all I can say is they published a paper describing 3D organization of chromatin. The exact link of that to massively multiplex RNA is something that I would need time to evaluate. This paper seems to be focused on chromatin. That is to say material within the nucleus. This is distinct from the kinds of molecules that were imaged in the 2015 paper. I'm not disputing this is from the same group.

For example, I don't see anything here about the kinds of probes that we used in the 2015 paper. Rather a thousand genomic loci.

Q Okay. Let's go to Exhibit 2007.

(10x Genomics Exhibit 2007 previously

marked for identification and retained by counsel.)

A Looks like another paper published well after the declaration, not in my bibliography, a paper that I can assert that I've seen but not familiar with.

Q This is also by a group that published the Chen paper?

A The last author is one.

Q So, yes, this is by the group that published the Chen paper, right?

A Looks like it, yes.

Q And this is extension of MERFISH to 3Ds and to RNAs in individual cells?

MR. HOLMAN: Objection. Scope.

A Looks like by 2023, these guys have figured it out. Again, well after the 2015 paper and the art disclosed therein. Which, again, suggests to me it was not obvious. It took the same group almost a decade. Almost a decade. Almost as if this wasn't obvious at all.

Q All right. Now with regard to

secondary consideration, you mentioned this multiple times. You reply -- you rely upon commercial success of CosMx indicia; is that right?

MR. HOLMAN: Objection. Form.

A So as I describe on paragraph 117, I bring up the commercial product Xenium and Bruker CosMX as evidence of industry praise, which I understand can be evident of a long-felt need. And then I go through, in my declaration, to establish the nexus between the claim -- between claim 36 and embodiments of these two devices.

Q Let me ask you a couple questions on that answer.

Do you rely upon commercial success of the CosMx as indicia of nonobviousness?

MR. HOLMAN: Object to form. Objection. Form. Scope.

A On page 114 of my declaration, I give my opinion on this part. The rapid growth in sales was the direct result of essential aspects of the '554 patent, namely, the complete

volumetric imaging systems' capability to provide high-resolution spatial data while streamlining the process from tissue handling to data interpretation.

So that's the sense in which I rely on the rapid growth in sales.

Q Now you mentioned the nexus requirement. What is the nexus requirement?

A My understanding of the nexus is that the particular parts of the claim in 36 have to be shown to be embodied in the systems.

Q So your understanding is that if certain elements -- you only need to have certain elements be embodied in the product, not the whole claim, just certain elements or the whole claim --

MR. HOLMAN: Objection. Form.

Q -- do you know?

A My understanding is encapsulated in paragraph 118. I understand the patentee is entitled presumption of a nexus between the objective indicia if the evident -- if the evidence is tied to a specific product that

embodies the claimed features and coexistence of them.

Q Okay.

A Then I go through in A, B, C, D, and E, examples of these -- examples.

Q Okay.

A Illustrate how I feel the Xenium and the CosMx embody the relevant claims in the '554 patent.

Q When you say "embody," what do you mean by that?

A What I mean by that is that somebody reading my declaration would understand the language of the claim has an analog and instrument.

Q Now, for a product to embody the claim, is it the case that every element of the claim needs to be present in the product, or is it good enough if only some of them are there?

Do you know?

MR. HOLMAN: Objection. Form.

A You're the lawyer. I'm afraid I don't

know the answer to that.

Q Okay.

A What I can say is that I go through claims A through E in sequence, in this declaration. And for each claim, pointing out where the material in that claim is embodied within the commercial instrument.

Q Claim elements?

A Claim elements. A, B, C, D, E.

Q So with regard to the CosMx product, and the temperature control apparatus of claim 36A2, you don't identify anything of the CosMx product that satisfies that, correct?

MR. HOLMAN: Objection. Form. Scope.

A Yes, in paragraph 121, I go through the temperature control apparatus system of claim 36 and how it's coupled with the sample, and then I explicitly show that in the Xenium 10x device, there is such a temperature control device.

I agree that is not showing for the CosMx.

Q Now let's go to paragraph 129. You

point out here that before Xenium and CosMx, research labs would have homebuilt setups that were unwieldy, sprawling, and laborious to assemble and maintain.

Do you see that?

A Yes, I do.

Q And your opinion is that the possibility of avoiding those unwieldy, sprawling, laborious systems is something that would have driven consumers to buy Xenium and CosMx; is that right?

A I think from what I know of homebuilt instrumentation, from my own experience, it's certainly the case that commercial adoption of the patents can speed adoption of the technology.

Q Wait. Hold on. Commercial adoption of the patent?

A Excuse me. Commercial embodiments of some technology can, relative to the homebuilt analog, speed adoption of the technology. So that's the sense in which I'm discussing, you know, a lab that -- if you are a lab and you were

interested in technology and you have to build it yourself and that homebuilt system was unwieldy, sprawling and laborious, if you're a biologist end user, chances are you're not going to use that. That's the sense in which I'm discussing the sentences in this page.

Q Is it your opinion that the fact that Xenium CosMx were not wieldy, sprawling, laborious is something that drove customer adoption?

A It's not a matter of my opinion, sir. This is what the customers, themselves, are saying on page 115. Those in the industry praised Xenium's streamlined workflow and ability to provide high-resolution spatial data, with quotes from the end users.

Q Now, the claims of the '554 patent, they don't have any requirements relating to sprawl, ease of assembly, maintenance, or unwieldiness, right?

MR. HOLMAN: Objection. Form.

A I think as I discussed before, that language is not in the patent's claim 36.

Q Not in any of the claims, right?
MR. HOLMAN: Objection. Form.
A Yes. The sprawling and unwieldy is not in any of the claims.
Q All right.
MR. HOLMAN: It's been about an hour.
MR. WALTER: Yeah, let's take a break. Sure.
(Recess taken from 3:37 p.m. to 3:45 p.m.)
(Exhibit 1080 marked for identification and attached to the transcript.)
BY MR. WALTER:
Q Okay. I've handed you a document that's been marked as Exhibit 1080. It's titled "CosMx SMI for Single-Cell Imaging."
This is a piece of promotion literature related to the CosMx product.
I think you testified earlier that you're not familiar with the features that Bruker promotes when it's trying to advertise the CosMx product; is that right?

A I've never seen this document before. Yeah, I'm not familiar with this certainly.

Q Let's go through some of these things.

If you take a look at page 1, it describes CosMx as a spatial multimovement single-cell imaging platform.

Do you see that?

A Spatial multimovement with tissue samples at cellular and subcellular resolution.

Q And it states there that it enables rapid quantification and visualization of up to 6,000 RNA and 64 validated protein analytes.

Do you see that?

A Yes, I do.

Q So, here they're promoting the number of analytes they can target?

A Uh-huh.

Q And the number of analytes, there's no minimum in the claims of the '554 patent, correct?

MR. HOLMAN: Object to the form.

A Well, I think as we discussed in claim 36E, there's language to the effect of one

or more nucleic acid molecules.

Q With regard to the claims of the '554 patent, the only requirement is that there be at least one nucleic acid molecule, right?

A Along with the rest of the claim, yes.

Q They're also promoting here that CosMx can do protein analytes, correct?

A I guess so. That's what it seems to say, 64 volumes of protein analytes.

Q And doing proteins is not within the claims of the '554 patent, right?

A Not within the claims of the -- not within the scope of claim 36E, which specifies identifying nucleic acid molecules.

Q It's not within the scope of any of the claims that are issued in this IPR proceeding, correct?

MR. HOLMAN: Object to the form. Foundation.

A All I can say is that that language doesn't appear in the claims, sir.

Q None of the claims cover protein,

correct?

A None of the claims use to word "protein analyte."

Q Or protein, right?

MR. HOLMAN: Object to form.

A I think that's right.

Q Now, if you go back to Exhibit 1080, the CosMx promotional material, it states it is the flexible, spatial, single-cell imaging platform that will drive deeper insights from cell atlasing, tissue phenotyping, cell-cell interactions, cellular processes, and biomarker discovery.

Do you see that?

A Yes.

Q Okay. These are specific applications that are doable with the CosMx SIM instrument?

MR. HOLMAN: Object to form. Scope.

A Those words are on this page, so I agree.

Q And the claims of the '554 patent, they don't have any requirements with regard to

particular applications?

MR. HOLMAN: Object to the form.

A These words are not in the claims. I'm not a lawyer, again, but my interpretation would be that they're limited by these words.

Q They're not limited in any particular applications, right?

A They certainly are limited -- certainly, we can agree they don't include these words in the claims.

Q But these particular applications, they're not requirements of any of the claims.

It's not as if the claim is if you do some other application, other than the ones listed here, you're not going to be infringing the patent, right?

MR. HOLMAN: Objection. Form. Scope.

A I'm not a lawyer, so I really couldn't say. I haven't considered that.

Q All right. Take a look at the second page. There's a section called "Sample Preparation," under item 1.

A Yes. I see that.

Q And under integrated readout, there's a picture of the instrument, and it says "robust in situ hybridization chemistry readout."

Do you see that?

A Yes, I do.

Q So here, they're advertising the hybridization chemistry that they use, correct?

A I don't know if that's correct or not, sir. I have never seen this document before. This is part of what I haven't seen before. It's literature of this advertisement, so I cannot say if it's correct or not.

Q Well, as someone skilled in the art who has opined on these instruments and how they're used and whether they meet the claims, you can surely look at this and understand what it's referring to when it's talking about in situ hybridization process, right?

MR. HOLMAN: Objects to form.

A I can surely look at these and assert that these are cartoons. Beyond that, I really

can't say without more analysis.

Q You can't say what in situ hybridization chemistry is being referred to there?

MR. HOLMAN: Objection. Form.

A From those words, I have no idea what the details are of the in situ hybridization chemistry. From the words on this page, in this document that I've never seen before, a document that is not scientific literature but, rather, a product brochure.

Q Okay. What about --

A A POSA wouldn't be able to say that either.

Q Now, you're not coming to this document in the vacuum. You've spent some time analyzing the CosMx instrument and you've gotten an understanding how it works because you prepared opinions how it meets the claim, right? Right.

A I have prepared opinions about CosMx as related to objective indicia. That's the relationship of my analysis of CosMx. Like I said

before, I've never seen this document. I don't know what these cartoons mean.

Q Okay.

A And in order to validate any of what you're saying, I would need to, like, dig in. This is not scientific, sir, this is a product brochure. You know, which is made by a company trying to sell a product. The relevance of this to the claims of the '554 patent are thin.

Q Now, this document, this is meant for eight-year-olds, right?

MR. HOLMAN: Objection. Form.

A There's a number of assumptions in your statement there. Like an eight-year-old would understand what in situ hybridization chemistry meant. I don't know of any 8-year-olds that know that. Do you?

Q No. That's my point.

Who is this document intended for?

A Sir, I have no idea who this is intended for.

Q This type of promotional literature

regarding instrumentation for spatial genomics, who would you say it's intended for, as someone skilled in the art and someone who is acting as an expert in this case and who is opining on this product?

MR. HOLMAN: Objection. Relevance. Objection. Scope.

A Sir, I don't honestly know who this document is intended for. I really don't know.

Q Could you hazard a guess?

MR. HOLMAN: Objection. Scope. Relevance. Scope.

A This could be useful for product managers, could be useful for scientists, this could be useful for people that work in universities. I mean, it could be useful for anybody who has any interest in hybridization chemistry, for all I know.

Q Now, with that in mind, and with your prior background, having analyzed the design and operation of these products, do you have any understanding of what it's referring to there when

it says in situ hybridization chemistry? Any idea whatsoever?

A You know, I understand what in situ hybridization chemistry means generally, in the context of nucleic acids. But again, having not seen this document before, having not known what exactly they mean, I would be speculating on the connection of that to what I understand about in situ hybridization chemistry.

Q Now, the in situ hybridization chemistry that they use in CosMx, whatever it is, they're stating in their promotional literature that they believe it's robust, right?

MR. HOLMAN: Objection. Form. Foundation.

A These words say "robust in situ hybridization chemistry," that's all I'm able to say.

Q All right. You would agree that Bruker is promoting its in situ hybridization chemistry to customers, right?

A Well, what do you mean by "promoting,"

sir?

Q They're advertising it. They're saying it's a beneficial feature. They're calling it robust, right?

A I mean, insofar as robust is advantageous, I believe you and I believe this is going to its intended audience.

Q Now, there's nothing in the claims that requires any particular hybridization chemistry at all, right?

MR. HOLMAN: Objection to form.

A I wouldn't go quite that far, sir. I mean, there's a reason that temperature control is cited in the claims because it's important in the process of hybridization, as detailed in the '554 patent.

Q Okay. Well, the 554 claims doesn't require any particular hybridization chemistry, right?

MR. HOLMAN: Objection. Form.

A The '554 claim, though, does require temperature control or heating and cooling, as

we've discussed, which is relevant for hybridization chemistry.

Q Are there any limitations in the '554 patent claims directed to hybridization chemistry?

A Those words don't appear. But as I said, taking the entire document in context, a POSA would have understood something about why the temperature control is important. And this is detailed in the '554 patent itself.

Q Okay. There's nothing in the claim that says that the method has to be performed using hybridization, is there? Maybe I'm missing something.

A There are no words including hybridization chemistry in the claims. But as I just said, there are elements of those claims that relate broadly, generally, to hybridization chemistry, as generally as the link you're trying to make between this and what Bruker is trying to do, for example.

Q So you agree that to satisfy the

claims, you have to be performing some form of nucleic acids hybridization, right?

MR. HOLMAN: Objection to --

A I didn't say that, sir. As I said before, hybridization chemistry doesn't appear in the claims.

Q Okay. Very good.

Let's go on, still on page 2, it states cloud -- refers to a cloud-based scalable computing and storage with interactive data viewer.

Do you see that?

A Yes, I see those words.

Q They're promoting the scalable computing and storage and the data viewer in connection with the CosMx product, right?

MR. HOLMAN: Objection. Scope. Form.

A Those words are on the page, sir.

Q Okay. There's nothing in the claims that requires scalable computing storage or interactive data viewer, is there?

MR. HOLMAN: Objection. Form.

Foundation.

A The claims do detail computing system in 36E. But the words "scalable" don't appear, for example. But it would be incorrect to say the claims have nothing to say about computing system.

Q Well, there's nothing in the claims that conveys that the computer system has to be scalable or that it has to have interactive active data viewer, right?

MR. HOLMAN: Objection. Form.

A The words "data viewer" and "scalable" don't appear once.

Q The concepts of a data viewer and scalable don't appear in the claims, do they?

MR. HOLMAN: Objection. Form.

A I mean, again, those words don't appear. But you're stretching a little bit when you say there's no indication at all of data or anything like that. I mean --

Q I didn't say that. I didn't say that.

A The claim specified determining three-dimensional positional information, which,

again, to a POSA, would apply some processing of the data.

Q So claims require a data viewer?

MR. HOLMAN: Objection. Form.

A Again, the words "data viewer" don't appear in the claims.

Q The concept of the data viewer isn't in the claims either, right?

MR. HOLMAN: Objection. Form.

A The words data viewer don't apply. The concept is a much trickier thing to pin down exactly.

Q Okay. So the claims require the concept of a data viewer, right?

A I didn't say that either.

Q Do you know, one way or another, whether the claims require a data viewer, either verbatim or in concept?

MR. HOLMAN: Objection. Form. Foundation. Scope.

A What I can definitively say is that scalable computing and data viewer don't appear,

those words don't appear in the claims.

Q Is that as far as you can go?

A That's as far as I'm willing to go.

Q Okay. That's fine. Our expert will go further.

Let's go to page 3.

There they have a testimonial from Dr. Holger Heyn of Spain.

Do you see that?

A Yes, I do.

Q And he is talking about the 1,000-plex gene panel.

Do you see that?

A Yes, I do.

Q So, here, 10x, through this testimonial, is promoting its 1,000-plex gene panel that it's made available to customers, right?

A 10x?

Q CosMx -- or, excuse me, Bruker.

MR. HOLMAN: Objection. Form. Scope.

A Those words are on the page, sir.

Q Now, there's nothing in the claims about gene panels, right?

MR. HOLMAN: Objection. Form.

A Again, those words don't appear in the claims.

Q And do you know, one way or the other, whether the concept appears in the claims? Can you say one way or the other or is that too tricky?

MR. HOLMAN: Objection. Form.

A Well, again, it's a little bit tricky because the claims do describe nucleic acid molecules. And as we both know, nucleic acid molecules relate to genes. So it's not like there's zero, zero of that.

Q Okay. Do you know, one way or another, whether the claims required, verbatim or conceptually, the concept of a gene panel?

MR. HOLMAN: Objection. Form. Foundation.

A Those words don't appear in the patent specification.

Q Okay. Will you say, one way or another, whether the claims require, verbatim or conceptually, conceptive gene panel?

MR. HOLMAN: Objection. Form. Scope.

A I'll stick by my previous statement. The words "gene panel" don't show.

Q Will you say, one way or the other, whether the claims require the concept of a gene panel?

MR. HOLMAN: Objection. Scope. Form.

A I'll repeat my previous answer, sir.

Q You can't say, one way or the other, whether the claims require, conceptually, a gene panel?

MR. HOLMAN: Objection. Scope. Form.

A That's as far as I'm willing to go.

Q Now, under "be the first to get."

Do you see that?

A Say again.

Q Halfway down the page it says "be the first to get."

Do you see that?

A I do see that, yes.
Q Okay. There's a series of features of CosMx that Bruker is promoting; there's five of them.
Do you see that?
A Yes, I do.
Q Okay. One is high-plex assays?
Do you see that?
A Yes.
Q The claims of the '554 patent don't require high-plex, in fact, they only require one, right?
MR. HOLMAN: Object to form and scope.
A The exact language in the '554 patent is determining three-dimensional positional information of said one or more nucleic acid molecules, as I said before.
Q Okay. The claims of the '554 patent don't require FFPE compatibility, right?
A Sir, I don't know what FFPE compatibility is.
Q You don't know what FFPE is?

A No.
Q Okay. You don't know what FFPE means?
A Maybe you can spell it out for me.
Q Formalin-fixed paraffin-embedded.
A Yes, thank you clarifying the record. Yes, I have heard of that.
Q Okay. The claims of the '554 patent don't require FFPE compatibility, right?
MR. HOLMAN: Objection. Form. Scope.
A Those words are not in the claims.
Q Is that concept in the claims? Do you know?
MR. HOLMAN: Objection. Form. Scope.
A Well, I wouldn't call it a concept.
Q What would you call it?
A I mean, it's a characteristic.
Q That characteristic isn't required by the claims, right?
A Certainly those words aren't in the claim.
Q The characteristic isn't required by the claim, right?

MR. HOLMAN: Objection. Form. Scope.

A Again, those words aren't in the claim, sir.

Q I'm asking something different. I'm not asking about the words. I'm asking whether the characteristic is required by the claim. Because you made the distinction between the word and the characteristic.

Is the characteristic required by the claims?

MR. HOLMAN: Objection. Form. Scope.

A I don't see any evidence for that.

Q True single-cell segmentation. Do you know what that's referring to?

A I understand the phrase "single-cell segmentation." I don't know what true single-cell segmentation is.

Q What is single-cell segmentation referring to?

A Single-cell segmentation, a POSA would understand, it refers to the ability to look at an image and then extract the portion of the image

that refers to the cell.

Q Now, is there anything in the '554 patent claims that requires the ability to do cell segmentation?

MR. HOLMAN: Objection. Form. Scope.

A I don't remember any such language in the '554 patent, sir.

Q Let's go the page 4 on the bottom. You can see that NanoString Bruker is promoting EZ sample preparation compatible with any sample type.

Do you see that?

A Page 4. Yes, I see those words, yes.

Q Okay. Is there anything in the claims of the '554 patent that requires EZ sample preparation?

MR. HOLMAN: Objection. Form. Scope.

A I don't believe I've seen EZ sample preparation anywhere in the document.

Q How about compatibility with any sample type? Is there anything in the claims that requires that the method be compatible with any

sample type?

MR. HOLMAN: Objection. Form. Scope.

A That phrase is also absurd. Nothing is compatible with any sample type.

Q Okay. But you agree there's nothing in the claims that requires compatibility with any sample type, right?

MR. HOLMAN: Objection. Form. Scope.

A I agree that compatible with any sample type isn't in the claims, but I don't see what relevance that has to our discussion.

Because I don't think that anything is compatible with any sample type. So it's -- yeah, I mean, it's irrelevant to comparison because it's an almost meaningless statement.

Q Let's go to page 8. You see there's a section that says "grant support CosMx SMI grant package"?

Do you see that?

A Yes, I see these words on the page.

Q Okay. You understand they're promoting the possibility of this grant package in trying to

sell the CosMx product?

MR. HOLMAN: Objection. Form. Scope.

A I don't know what that means, sir.

Q You wouldn't purport to know why it is the customer buy the CosMx product, right?

MR. HOLMAN: Objection. Form.

A The only thing that I know about customers and the CosMx product is what I've written in the declaration, sir, which is stated clearly that we've discussed. That's my -- that's the extent of what I think about what customers have to say about these products and how they lead to objective indicia.

Q That's it? Nothing more?

A Exactly what I say in paragraph 130.

Q Okay.

MR. HOLMAN: Generally object to Exhibit 1080, FRE-401, 403, 802, and 901.

(Exhibit 1081 marked for identification and attached to the transcript.)

Q Let's go to 1081.

All right. This is kind of the same

thing except it's for Xenium, which is the 10x product.

If you look at the first page -- I'm sorry, page 2. At the very top, it states "The current version of the assay uses DAPI nuclear stain as the tissue morphology marker to inform platform segmentation of the cell borders."

Do you see that?

A Yes, I do.

Q So this is -- here, they're promoting the use of the DAPI nuclear stain?

A So, I would like say again, I've never seen this document. I don't understand the relevance of this to the case. And as far as your assertion that they're promoting the DAPI nuclear stain, I have no idea if Xenium or 10x uses the DAPI stain or not.

Q You can't tell from this document?

A No. Neither can you.

Q I think I can.

A I think you can't.

Q All right. Do you know what the DAPI

nuclear stain is?

A Sure, I know what the DAPI nuclear stain is.

Q And there's nothing in the claims of the '554 patent requiring that kind of nuclear stain or any nuclear stain at all, right?

MR. HOLMAN: Objection to form.

A Those words are not in the claims of the '554 patent.

Q How about the concept? Is that in the claims of the '554 patent? Or if you want to use your words, characteristic. Is that characteristic in any of the claims of the '554 patent?

MR. HOLMAN: Objection to form.

A Not to my recollection.

Q It goes on and states the number of targets is currently limited to, approximately, 500 genes, though future panels are promised 1,000 to 5,000-plus and will also allow simultaneous profiling of protein expression targets as well.

Do you see that?

A I see those words yes.
Q So, here, they're looking at the number of targets they can hit?
MR. HOLMAN: Objection. Form. Scope.
Q Right?
A Those words are on the page, sir. I mean, again, having never seen this document before, I don't understand the motivation of Xenium. I mean, they're saying that as of whenever this document was published, the current (indiscernible) 500 genes. And in the future, they may do more.
Q You've said many times you're not a lawyer, right?
A It is true that I'm not a lawyer, sir.
Q Okay. And so, you know, it's possible this might be relevant to some issues that you don't know anything about because you're not a lawyer, right?
A It's true that I'm not a lawyer. And also what you said is true.
Q Okay. So there's nothing in the claims

of the '554 patent, we've talked about this many times, that requires any particular number of targets, except that it be at least one, right?

MR. HOLMAN: Objection. Form.

A Playing a little bit fast and loose with the targets. The exact language is determining three-dimensional positional information of said one or more nucleic acid molecules.

Q Okay. In terms of the number of nucleic acid molecules, there's no requirement except that there be at least one, right?

A One or more than one, correct.

Q Now, this also is promoting the simultaneous profiling of protein expression targets, right?

MR. HOLMAN: Objection. Form. Scope.

A That's what it says, sir.

Q That's not in the claims of the '554 patent, right?

MR. HOLMAN: Objection. Form. Scope.

A That language is not in the

'554 patent.

Q Okay. Now, at the bottom of that first paragraph, right above the image, it says data is easily viewable, provided desktop tools and compatible with a rapidly developing array of downstream third-party analysis tools.

Do you see that?

A Yes, I see those words.

Q So this is promoting the desktop data viewer that's available at Xenium and, also, its compatibility with a range of third-party analysis groups, right?

MR. HOLMAN: Objection. Form. Scope.

A Those words are on the page, sir. But your assertion whether or not it's true or false, I couldn't say.

Q And you agree that the claims in the '554 patent don't require an easily viewable data viewer or compatibility with downstream third-party analysis tools, right?

MR. HOLMAN: Objection to form. Scope.

A That language is not in the claims.

Q If you go down to the second bullet, under key features.

A Uh-huh.

Q It says "Sensitive and Accurate Chemistry: Padlock probe and rolling circle amplification promote greater specificity and allow better sensitivity."

Do you see that?

A I see those words, yes.

Q Do you know what padlock probe and rolling circle amplification is?

A I know what rolling circle amplification certification is. You'll have to remind padlock probe. Although I have heard of them, I don't know exactly what that is.

Q In this bullet, they're promoting use of the padlock probe and the rolling circle amplification mechanics of the product, right?

MR. HOLMAN: Objection. Form. Scope. Foundation.

A I have no idea, sir. I mean, it's a vague statement. I don't know what greater

specificity and better sensitivity mean. Greater specificity and better sensitivity relative to what?

Q And you agree that there's nothing in the claims of the '554 patent that requires use of padlock probes or rolling circle amplification, right?

MR. HOLMAN: Objection. Form. Scope.

A I agree that those words are not in the claims.

Q There's a bullet down at the bottom that says speed. "Short sequencing time and onboard image data processing provide viewable data quickly."

Do you see that?

A I do.

Q So this is promoting the advantage of being able to view your data quickly, right?

MR. HOLMAN: Objection. Form. Scope.

A That's what these words suggests, yes.

Q There's nothing in the claims of the '554 patent that requires that you be able to view

the data quickly, right?

MR. HOLMAN: Objection. Scope. Form.

A There's no -- those words are not in the '554 patent.

Q And the concept's not there either, right?

MR. HOLMAN: Objection. Form. Scope.

A As far as viewing data quickly, I couldn't say.

Q You can't say, one way or another, whether that concept is in the claims of the '554 patent?

MR. HOLMAN: Objection. Form. Scope.

A All I can say, again, is that those words are not in the claims that I reviewed.

MR. HOLMAN: I'm going to object, generally, to Exhibit 1081. FRE-401, 402, 403, 901, and 802.

Q Let's go to paragraph 118 of your declaration.

A 118, sir?

Q Yeah.

A 118, yes.

Q Okay. You state here "I also understand that even if a commercial embodiment is not coextensive with claimed features in a patent, then objective indicia will still have a nexus if the objective indicia evidence is the direct result of the claimed invention's unique characteristics."

Do you see that?

A Yes, I do see that sentence.

Q Okay. Are there any unique characteristics within any of the claims of the '554 patent?

A Well, as I point out in my declaration, there are characteristics that are not covered by Dr. Czymmek's attempt to combine Chen, Shen, and Cai. One of which is the temperature control we discussed before, another is the ability to get to something like 3D MERFISH, which Dr. Czymmek asserts but isn't true, for reasons that I detail.

Q Okay. Any others?

A Those are the only ones that come to

mind most readily?

Q Now, was the ability to do temperature control, was that something that was known in the prior art, prior to 2015?

MR. HOLMAN: Objection. Form.

A I think we've been over this before. The point is that temperature control, as defined in the '554 patent, is not the same as temperature control as disclosed by Czymmek.

Q I guess in that sentence, let's adopt, for the moment, your definition of temperature control. Was that something that was in the prior art, prior to 2015?

A Also as we've discussed, the POSA would have known that you can heat and cool. But here, what's relevant is claim 43, and the context of the entire claim 36. It's that combination that is central to the '554 patent.

Q What combination?

A The dependent claim 43 along with the independent claim 36.

Q Oh, okay. So explain to me what you

meant about that, that the combination of deep claim and an independent claim is central to the '554 patent.

What do you mean by that?

A Really what I mean is described in my declaration, that paragraph 115 is what I'm getting at, that the dependent claim requires all the limitations on the claim for which it depends. So each of the claim, 37 to 70, depend directly or indirectly from claim 36.

My point is that all heating and cooling are known before. What's relevant here is heating and cooling in the context of claim 36.

Q So when you say "unique characteristics of the claim," you're not saying heating and cooling by itself, you're saying the claim as a whole, right?

MR. HOLMAN: Objection to form.

A What I'm saying about heating and cooling is the sense in which it's used in the '554 patent is different than the sense in which Czymmek used it.

And so, in that sense, you can't get that from what Czymmek describes in his declaration.

Q Okay. I'm asking something different. I understand your contention about what Czymmek relies upon. You say that's not in Shen, Chen, and Cai. I get that. I'm asking something different.

Was the concept of temperature control, as you believe it's defined in the '554 patent, something that was present in the prior art prior to November 2015?

A And as I've said before, heating and cooling were known before. But if we read claim 36 in its entirety, as well as the other claims, this is something that was not known.

Q Okay. So now I'm going to move on my related question here. I was asking about the unique purposes of the claim.

You're not contending that heating and cooling, by itself, was something that was a new or unique characteristic. What you're contending

was new is the claim as a whole, right?

Is that your contention?

MR. HOLMAN: Objection. Form.

A Right. What I contend in the claim is exactly what I describe in paragraph 115 of my declaration. The relevance of the heating and cooling that I bring up is because CosMx and the Xenium is contained at pages 103 through 114. That is the objective indicia point.

So heating and cooling are aspects -- the temperature control aspects, excuse me, are aspects that I describe in the context of the claim. Its nexus would be in the convention, as described in paragraph 121.

Q Did you ever look for any promotional literature to see if either 10x or Bruker advertised temperature control as one of the key features of the product?

A So the only product literature that I remember seeing is the one in which you've just delivered to us. That's the first time that I've seen anything like this, this level of product

literature.

Q Okay. Now, I think the other unique feature you identify was doing multiple targets in 3D.

Is that the other unique feature you think is in the claims?

MR. HOLMAN: Objection. Form.

A Determining three-dimensional positional information of said one or more nucleic acid molecules is not covered effectively by Czymmek in his attempt to combine Chen, Shen, and Cai.

Q But looking at multiple nucleic acid molecules in 3D, that wasn't the prior art, right? We looked at a number of examples today, right, including from your own publications, right?

MR. HOLMAN: Objection. Form. Foundation.

A And as we discussed, when we discussed those publications, they have, essentially, no relevance to the case at hand.

Q Because they're not like MERFISH? Is

that your contention?

A Well, a number of them were published after 2015.

Q Well, a lot of them weren't.

A And then for the other ones, it goes back to what we were discussing earlier, that in order to use those methods effectively, you have to assume things about the sample, right? So if we take the example of the Drosophila, for example, right, this is a few types of nucleic acids in the Drosophila embryo. It's almost no relevance to any of the discussions in Czymmek regarding massive and multiplex MERFISH, getting to 3D MERFISH with Shen and Cai.

Q Now, if the person of skill in the art were trying to use claim 36, you don't contend that claim 36 gives you, like, a recipe and you can easily apply it to any sample without having to know something about the sample and make some judgments, right? You don't contend that, do you?

MR. HOLMAN: Objection. Form.

A My opinions are confined to the

declaration and I have very little to say about speculating claim 36.

Q I'm asking you here now. As someone who has thought about claim 36 and someone who's an expert in this space and providing opinions on obviousness. You don't contend that claim 36 provides sort of general-purpose recipe that a person skilled in the art could apply to any type of sample type without having to make some sort of judgments about what type of microscopy modality to use or other things like that, right?

MR. HOLMAN: Objection. Form. Foundation.

A It's a very broad question. And to answer that, I would have to really study claim 36 in that vein. Again, the comments that I've provided to you in this declaration really have much more to do with refuting Czymmek than speculating on what claim 36 does or does not allow.

Q Okay.

MR. WALTER: I think I'm done with my

questions for now. I'll let you guys redirect and I'll come back with more questions, if it seems necessary.

MR. HOLMAN: Let's go off the record.

(Recess taken from 4:22 p.m. to 4:57 p.m.)

MR. HOLMAN: Back on the record. Dr. Shroff, we have no questions for you. Thank you for your time. This deposition is over.

THE WITNESS: Okay. Thank you.

(Off the record at 4:57 p.m.)

ACKNOWLEDGMENT OF DEPONENT

I, HARI SHROFF, PH.D., do hereby acknowledge that I have read and examined the foregoing testimony, and the same is a true, correct and complete transcription of the testimony given by me and any corrections appear on the attached Errata sheet signed by me.

_____ _____

(DATE) (SIGNATURE)

CERTIFICATE OF SHORTHAND REPORTER - NOTARY PUBLIC

I, Judith E. Bellinger, Certified Reporter and Notary Public within and for the District of Columbia do hereby certify:

That HARI SHROFF, PH.D., the witness whose deposition is hereinbefore set forth, was duly sworn by me before the commencement of such deposition and that such deposition was taken before me and is a true record of the testimony given by such witness.

I further certify that the adverse party, 10X GENOMICS, was represented by counsel at the deposition.

I further certify that the deposition of HARI SHROFF, PH.D., occurred at the offices of STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C., 1101 K Street NW, Washington, DC 20005, on Tuesday, February 4, 2025, commencing at 9:02 a.m. EST.

I further certify that I am not related to any of the parties to this action by blood or marriage, I am not employed by or an attorney to

any of the parties to this action, and that I am in no way interested, financially or otherwise, in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 15 day of February, 2025.

My commission expires:
January 1, 2027

Judith E. Bellinger

_____

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