

In the Matter Of:

Parse Biosciences, Inc. v

10X Genomics, Inc.

JOHN QUACKENBUSH, PH.D.

February 28, 2024



UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.,	)	
	)	
Petitioner,	)	
	)	Case No.
v.	)	IPR2023-00876
	)	
10X GENOMICS, INC.,	)	
	)	
Patent Owner.	)	

- - -
Wednesday, February 28, 2024
- - -

Videotaped deposition of JOHN
QUACKENBUSH, Ph.D. was taken before Elizabeth M.
Kondor, Certified Court Reporter and Notary
Public, on the above date, commencing at 9:05
a.m.

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1	VIDEOGRAPHER: We are now on the
2	record. My name is Jonathan Perry. I'm a
3	videographer retained by Lexitas.
4	This is a video deposition for the
5	United States Patent and Trademark Office,
6	before the Patent Trial and Appeal Board,
7	IPR No. 202300876.
8	Today's date is February 28, 2024.
9	The time is approximately 9:05 a.m.
10	We are at the offices of Weil Gotshal
11	& Manges, 2001 M Street Northwest in
12	Washington, D. C.
13	This is being taken in the matter of
14	Parse Biosciences, Incorporated versus 10x
15	Genomics, Incorporated.
16	The name of the witness is John
17	Quackenbush, Ph.D.
18	And would counsel present please
19	introduce themselves and state whom they
20	represent.
21	MR. REINES: Ed Reines, Weil,
22	Gotshal, Parse.
23	MS. RAYMOND: Megan Raymond from
24	Groombridge Wu Baughman & Stone for 10x.
25	With me is Josh Reich.

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1	VIDEOGRAPHER: And the court reporter
2	is Elizabeth Kondor, also with Lexitas.
3	Would you please swear in the
4	witness.
5	J O H N Q U A C K E N B U S H, P h. D.,
6	having been first duly sworn, testified as
7	follows;
8	EXAMINATION BY MR. REINES:
9	Q. Please state your name for the
10	record.
11	A. My name is John Quackenbush,
12	Q-U-A-C-K-E-N-B-U-S-H.
13	Q. You understood that today's
14	deposition is to address your opinions given in
15	this case?
16	A. Yes, I do.
17	Q. And you did your best to prepare for
18	the deposition; is that correct?
19	A. Yes, I did.
20	Q. What did you do?
21	A. I reviewed the document cited in my
22	report, the expert report. I had a meeting
23	yesterday with the attorneys representing 10x,
24	and had, I believe, one short phone or Zoom
25	conference with Josh on Friday and then a

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1 half-hour Zoom conference with him on Monday. 2 Q. How much time have you invested in 3 being prepared for the deposition? 4 A. So I was here most of the day 5 yesterday. And then spent some time over the 6 weekend and time in the week leading up. I 7 don't know exactly how long. 8 Q. More or less than 30 hours? 9 A. Probably less, but I'd have to look. 10 Q. More or less than 20 hours? 11 A. Probably more, but, again, I'd have 12 to take a look. 13 Q. So your best estimate currently 14 sitting here now is that you spent about 20, 30 15 hours preparing for the deposition; is that 16 correct? 17 A. That's a reasonable guess, but the 18 exact tally, I don't know. 19 VIDEOGRAPHER: Off the record at 20 9:10. 21 (Off the record.) 22 VIDEOGRAPHER: On the record at 9:11. 23 BY MR. REINES: 24 Q. I'd like to show you Exhibit 2013, 25 which is your declaration.	1 sometime after Dr. Cooper's report, I believe 2 after his deposition, although I don't know 3 exactly when, because this report is a response 4 to Dr. Cooper's report in this PTAB matter. 5 Q. When you started working on your 6 opinions in this case set forth in your 7 declaration, did you have the Cooper deposition 8 transcript? 9 A. I don't recall exactly when I started 10 working. I don't recall when Dr. Cooper was 11 deposited. 12 In putting this together, I did have 13 access to Dr. Cooper's deposition transcript, 14 but I don't know at what point I received it in 15 the process. 16 Q. If you turn to page 7 of your 17 declaration, please. 18 And do you see the section on 19 "Obviousness" setting forth the legal standard? 20 A. Yes, I do. 21 Q. Where did you receive this 22 information? 23 A. So I'm not an attorney or a patent 24 agent, and so I was instructed as to the meaning 25 of obviousness by the attorneys representing
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1 How much time did you expend 2 preparing the opinions in this declaration and 3 the declaration itself? 4 A. Sitting here today, I couldn't tell 5 you. 6 Q. What's your best estimate? 7 A. I don't know. Probably more than 40 8 hours, but I couldn't tell you. I'd have to 9 look back at my records. A lot of this came 10 together at a very busy time of year. 11 Q. When did you first receive the 12 assignment to work on this declaration? 13 A. I don't recall the exact date. 14 Q. What's your best estimate? 15 A. I couldn't give you an estimate. I 16 really don't know. 17 Q. Was it in 2023? 18 A. It was almost certainly at some point 19 in 2023. 20 Q. Was it before or after the summer of 21 2023? 22 A. So I was contacted by the attorneys 23 in Groombridge and asked if I would be willing 24 to work on this. I really started working on 25 this report, though, after Dr. Cooper's --	1 10x. 2 Q. When did that happen? 3 A. I don't recall the exact date. It 4 happened early in our discussions. 5 Q. Was this after you received the 6 Cooper report? 7 A. I don't recall exactly when. I've 8 worked as an expert witness a number of times 9 and I'm familiar with the concept of 10 obviousness, in anticipation. But this 11 particular set of instructions reflect the 12 instructions and information I was provided by 13 the attorneys from Groombridge. 14 Q. What was the assignment that you 15 received in this case? 16 A. So Dr. Cooper had filed a motion 17 before the PTAB, and I was asked to respond. 18 So now thinking back, I may have 19 submitted earlier declarations. I don't recall 20 -- I don't recall the earlier work I did, but 21 the assignment for this report in particular was 22 a response to Dr. Cooper's report that was filed 23 before the PTAB. 24 Q. And in terms of how you responded in 25 terms of what portions of Dr. Cooper's report

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1 you contested and the basis for contesting it, 2 was that from you or was that from the 3 attorneys? 4 A. So I had the opportunity to read 5 through Dr. Cooper's report to try to understand 6 it to the best of my ability, given what he was 7 presenting; to read over the patents since he 8 was stating that elements of the patent were 9 rendered obvious; to look at the references that 10 Dr. Cooper cited. And then I had a series of 11 discussions with the attorneys about the 12 different theories that Dr. Cooper had presented 13 about the obviousness of the patent given the 14 references that he cited. 15 Q. In terms of how you responded to 16 Dr. Cooper's report regarding what you contested 17 and the basis for contesting it, did that come 18 from you or did that come from the attorneys? 19 MS. RAYMOND: Objection. I just 20 caution the witness not to reveal the 21 substance of conversations with attorneys. 22 A. It arose during discussions with the 23 attorneys about what was represented in 24 Dr. Cooper's report. We spent a lot of time 25 trying to figure out together what Dr. Cooper	1 the attorneys? 2 A. I'm not sure I understand the 3 question. 4 Q. Were there any limits? Is there 5 anything that you wanted to include or paths you 6 wanted to follow that you were told not to? 7 A. No. 8 Q. And who decided which part of 9 Dr. Cooper's report you would be contesting and 10 which you wouldn't be contesting? 11 MS. RAYMOND: Objection. 12 I just caution the witness not to 13 reveal the substance of communications with 14 the attorneys in preparing this report. 15 A. So I'm not sure -- I'm not sure what 16 you're asking. 17 I don't contest Dr. Cooper's current 18 employment or where he's working. It was really 19 looking at the substantive arguments he made 20 that I tried my best to respond to. 21 Q. Who decided whether you contested 22 particular substantive arguments made by 23 Dr. Cooper or not? 24 A. I believe we responded to all the 25 substantive arguments that Dr. Cooper advanced.
Page 11	Page 13
1 meant when he advanced certain ideas. There are 2 places in his report that we struggled to try to 3 make sense of. 4 Q. So you didn't understand Dr. Cooper's 5 theories in total, correct? 6 MS. RAYMOND: Objection to form. 7 A. I wouldn't characterize it that way. 8 To the best of my ability, I analyzed what 9 Dr. Cooper presented. There are places where 10 Dr. Cooper seems to leave things out, and so, to 11 the best of my ability, I tried to respond to 12 that. 13 And in preparing my responses, I 14 actually looked at a variety of different 15 alternatives and presented those in different 16 subsections of round 1 as I really tried to go 17 through and understand the potential arguments 18 that Dr. Cooper was making. 19 Again, there are places where 20 Dr. Cooper I think has incomplete 21 representations of how certain references 22 including Linnarsson and McCloskey might be 23 combined. 24 Q. Was there any constraint put on you 25 in how you responded to Dr. Cooper's report by	1 Q. Okay. 2 Dr. Cooper's report includes a number 3 of opinions, correct? 4 A. You might characterize it that way. 5 Q. There's -- Dr. Cooper's report has 6 opinions with bases and grounds in it, correct? 7 A. That is correct, yes. 8 Q. Okay. 9 And some of them you contest and some 10 of them you don't contest, right? 11 A. I don't recall grounds that we didn't 12 -- or arguments that Dr. Cooper made that I 13 didn't contest. If you'd like to point me to 14 those in Dr. Cooper's report, I'd be happy to 15 refresh my memory. 16 Q. Okay. 17 So you think it may be that you 18 contested every point that Dr. Cooper made in 19 his report? 20 A. Again, I don't have Dr. Cooper's 21 report in front of me. I think I responded to 22 the substantive arguments that Dr. Cooper made. 23 Q. My question is, do you believe you 24 contested every point, substantive point made by 25 Dr. Cooper?

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1 MS. RAYMOND: Objection to form. 2 A. Sitting here today, I don't know what 3 you would characterize as a substantive point 4 that I didn't respond to. And I believe I 5 reserved my right to respond to -- to amend my 6 report if there was anything that I missed. 7 Q. Is there any aspect of Dr. Cooper's 8 substantive analysis with which you agreed? 9 A. If you can point me to different 10 places in my report where I stated that, I'd be 11 happy to discuss it. 12 There are -- you know, I don't know 13 what you would consider substantive and places 14 where you believe I didn't contest Dr. Cooper's 15 opinions. 16 Q. Okay. 17 So you're not comfortable saying that 18 there's any point of substance that you agree 19 with Dr. Cooper on without going through your 20 report? 21 MS. RAYMOND: Objection to form. 22 A. I don't understand what you consider 23 to be of substance, and so I really can't 24 provide you with an informed opinion. 25 I believe I responded to Dr. Cooper's	1 I respond to Dr. Cooper's arguments 2 about obviousness, which were largely 3 combinations of two references, a Linnarsson 4 patent and an article by McCloskey. And then 5 with regard to claim 5, those two references and 6 an article by Hug. 7 Q. Please try to answer my question. 8 What did you do to investigate 9 whether there were objective indicia supporting 10 your position? 11 MS. RAYMOND: Objection. Asked and 12 answered. 13 A. So I believe I answered that question 14 to the best of my ability -- or to the best of 15 my recollection. 16 I didn't provide any opinions here 17 about objective indicia. I don't believe 18 Dr. Cooper offered any opinions regarding 19 objective indicia. 20 Q. Did you do anything to investigate 21 whether there were objective indicia supporting 22 10x? 23 A. I don't believe -- I think I answered 24 the question twice. I don't believe I provided 25 any opinions in my report regarding objective
Page 15	Page 17
1 substantive arguments and provided grounds for 2 my analysis. 3 Q. And the reason you can't answer my 4 question is because you don't understand what I 5 mean by "substance"; is that correct? 6 A. You could have -- you could consider 7 some things substantive. I don't know -- I 8 don't know what you're considering. 9 Q. All right. 10 If you turn to paragraph 19 of your 11 report. 12 Do you have that in front of you? 13 A. I do, yes. 14 Q. You understand that these are the 15 four factors that are the part of the 16 obviousness determination? 17 A. Yes, that's my understanding. 18 Q. And in terms of the fourth factor, 19 objective indicia, what did you do to 20 investigate whether there was objective indicia 21 supporting your position? 22 A. So to the best of my recollection, I 23 didn't offer any opinions on objective indicia. 24 I don't believe Dr. Cooper provided any 25 arguments regarding that.	1 indicia. My report was a response to 2 Dr. Cooper, and I don't believe Dr. Cooper 3 himself offered any opinions regarding that. 4 Q. The reason why, as the patent owner, 5 you didn't include objective indicia opinions in 6 your report is because Dr. Cooper didn't; is 7 that what you're saying? 8 A. I was responding -- as I said 9 earlier, I was responding to Dr. Cooper's 10 arguments about the obviousness and validity of 11 the '918 [sic] patent. And I don't believe 12 Dr. Cooper provided any arguments that I needed 13 to respond to. 14 Q. Is that the reason why you didn't -- 15 well, let me ask you this. Try to answer as 16 directly as you can. 17 Did you investigate whether there was 18 objective indicia of nonobviousness supporting 19 your position since you listed that as one of 20 the four factors used to make an obviousness 21 determination? 22 A. So my assignment in preparing this 23 report was to respond to Dr. Cooper's opinions 24 that he had provided in his report. I don't 25 believe Dr. Cooper provided any objective

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1 indicia arguments. And so in not responding -- 2 in not having to respond to those, I simply 3 didn't include those in my report and didn't 4 spend time investigating them. 5 Q. If you turn to paragraph 23, do you 6 see where you state, "...the Board must consider 7 objective 'indicia' or factors..." 8 A. Yes. 9 Q. And do you see where you say, "The 10 presence of such factors is evidence of 11 nonobviousness"? 12 A. Yes. 13 Q. And given that you stated that the 14 board must consider objective indicia of 15 nonobviousness, how come you didn't even 16 investigate that? 17 A. So I believe the attorneys 18 representing 10x may have presented that in 19 their own briefs. 20 Again, my assignment was not to 21 provide a comprehensive analysis but really to 22 provide a comprehensive response to Dr. Cooper's 23 allegations of obviousness. So given the fact 24 that Dr. Cooper didn't present any arguments 25 about objective indicia, I had nothing to	1 all the motions that have been filed and the 2 briefs that have been filed before the PTAB. 3 I can tell you that my assignment was 4 to respond to Dr. Cooper, and I don't believe 5 Dr. Cooper provided any opinions regarding the 6 objective indicia. 7 I'd be happy to look at his report if 8 you provide it to me and see if he does provide 9 those opinions. 10 Q. In terms of who has the burden of 11 going forward on objective indicia, you 12 understand that that's the party that is the 13 patent owner? 14 A. I don't know who carries what burdens 15 in what circumstances. 16 Q. Do you understand that if the patent 17 owner wants to rely on objective indicia of 18 nonobviousness, that it needs to present 19 evidence of that? Do you have at least that 20 understanding? 21 A. I would assume that if a party wanted 22 to rely on some criteria, they would have to 23 provide that. But, again, I'm not a patent 24 attorney or patent agent. 25 Q. Are the claimed inventions of the
Page 19	Page 21
1 respond to. 2 Q. In other cases where you were 3 responding to an obviousness analysis, you've 4 presented opinions regarding objective indicia, 5 correct? 6 A. I may have. It would depend on the 7 case. I've rendered opinions about obviousness 8 both in district court and before the PTAB and I 9 don't recall -- I don't recall all the 10 circumstances in which I provided those 11 opinions. 12 Q. My question wasn't about all the 13 circumstances. 14 In fact, you have given objective 15 indicia testimony in response to an obviousness 16 report, correct? 17 A. I almost certainly have. It would 18 depend on the circumstances whether or not I 19 believe it was necessary. 20 Q. And did you reach a conclusion here 21 it was unnecessary to consider objective 22 indicia? 23 A. I wouldn't say it's unnecessary. 24 Again, the PTAB is likely to consider that in 25 evaluating the '918 [sic] patent. I don't know	1 '981 patent commercially successful? 2 MS. RAYMOND: Objection. Scope. 3 A. So I haven't done an analysis of the 4 '918 [sic] patent. I don't know if 10x claims 5 they're practicing the invention of the '918 6 [sic] patent. I didn't provide an opinion about 7 that, and I'm not prepared to offer an opinion 8 today. 9 Q. Was there a long-felt need for the 10 claimed inventions of the patent-in-suit? 11 MS. RAYMOND: Objection. Scope. 12 A. I didn't provide any opinions about 13 that, and I'm not prepared to offer an opinion 14 today. 15 Q. Do the claimed inventions of the 16 patents-in-suit -- can you identify any 17 unexpected results offered by the claimed 18 inventions of the patent -- 19 MS. RAYMOND: Objection. Scope. 20 Q. -- of the '981 patent? 21 A. I haven't performed that analysis, 22 and I'm not prepared to offer an opinion today. 23 I haven't formed that analysis in the context of 24 this matter. 25 Q. Are you aware of any -- can you

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1 identify any copying of the claimed inventions 2 of the patents-in-suit? 3 MS. RAYMOND: Objection. Scope. 4 A. Again, I have not done that analysis 5 in the context of the matter we're discussing 6 today, and I'm not prepared to provide an 7 opinion. 8 Q. Can you identify any praise by those 9 in the field for the claimed inventions? 10 MS. RAYMOND: Objection. Scope. 11 A. So I don't believe Dr. Cooper offered 12 any opinions for me to respond to. I didn't do 13 that analysis in the context of the matter we're 14 discussing today, and I'm not prepared to offer 15 any opinions now. 16 Q. Have you ever seen a patent 17 challenger include objective indicia analysis in 18 their opening report? 19 A. To the best of my recollection 20 sitting here today, I don't know. 21 Q. Can you identify any instance where 22 you've ever seen that? 23 A. I haven't looked back at other 24 matters that I've been involved in, and so I 25 couldn't give you an informed answer.	1 MS. RAYMOND: Objection to the form. 2 A. My understanding is that the board -- 3 that this is part of what the board is required 4 to do. 5 Again, I'm not an attorney. I don't 6 know what other arguments have been made in this 7 case about the objective indicia. So I was 8 asked to respond to Dr. Cooper's arguments, and 9 those are the responses that are contained in my 10 report and that I'm happy to discuss today. 11 Q. Please focus on my question. 12 Who made the decision that you 13 weren't to include objective indicia supporting 14 the nonobviousness of the patent in your report? 15 MS. RAYMOND: Objection. Form. 16 A. So I worked with the attorneys from 17 Groombridge, who are representing 10x, in 18 preparing my report. And in doing that, my 19 assignment was to respond to Dr. Cooper's 20 arguments, which I believe I provided a fulsome 21 response in the report, and I'm happy to discuss 22 those. 23 Q. And as to whether or not objective 24 indicia of nonobviousness were part of the 25 response to Dr. Cooper's opinions included in
Page 23	Page 25
1 Q. Did you investigate whether there was 2 a long-felt need for the claimed inventions? 3 A. I believe I answered that question. 4 My assignment here was to respond to 5 Dr. Cooper's arguments. I don't believe I did 6 that analysis, and it doesn't appear in my 7 report, so I'm not prepared to offer an opinion 8 today. 9 Q. Do you believe that objective indicia 10 of nonobviousness, if they existed, would be an 11 appropriate response to the opinions provided by 12 Dr. Cooper? 13 MS. RAYMOND: Objection. Scope. 14 A. So you're asking me to render what I 15 believe is a legal opinion. I'm not prepared to 16 do that. 17 I provided a pretty comprehensive 18 analysis of Dr. Cooper's report, and I'm happy 19 to discuss those opinions I rendered with you 20 today. 21 Q. Who made the decision that you 22 weren't including objective indicia and an 23 objective indicia analysis in your report when 24 you state, "The Board must consider certain 25 objective 'indicia'..."?	1 your report, whose decision was that? 2 A. I don't know if there were responses 3 or not. I'm not a party to all of the documents 4 that have been filed in this case. I was asked 5 to respond to Dr. Cooper's theories about 6 obviousness and those are what I provided in my 7 report that I'm happy to discuss. 8 Q. Who made the determination that 9 including objective indicia of nonobviousness 10 was not a part of the response to Dr. Cooper's 11 opinions -- 12 MS. RAYMOND: Objection to form. 13 Q. -- for your declaration that you 14 prepared? 15 MS. RAYMOND: Objection. Form. 16 And I caution the witness not to 17 reveal privileged conversations. 18 A. So in preparing my report, I worked 19 with the attorneys from Groombridge. We 20 carefully analyzed Dr. Cooper's report, the 21 patents and a number of other documents that are 22 cited in my report and arrived at the opinions 23 that I've set out here. 24 Q. Was it outside the assignment that 25 you were given in this case to consider

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1 objective indicia of nonobviousness? 2 A. I believe that my response and my 3 assignment was to respond to Dr. Cooper, and I 4 believe my response is very thorough and 5 complete and demonstrates that Dr. Cooper's 6 opinions about obviousness are incorrect. And 7 I'd be happy to discuss those today. 8 Q. Was it inside or outside your 9 assignment in this case to consider objective 10 indicia of nonobviousness? 11 MS. RAYMOND: Objection. Form. 12 A. I met with the attorneys from 13 Groombridge. My assignment was to respond to 14 Dr. Cooper. And I believe I provided a fulsome 15 response, and I'd be happy to discuss the 16 response that's included in my report. 17 Q. Can you state one way or the other, 18 answering as specifically as you can, whether 19 considering objective indicia of nonobviousness 20 was inside or outside your assignment in this 21 case? 22 MS. RAYMOND: Objection. Form. 23 A. I was asked to respond to 24 Dr. Cooper's theories about obviousness. I 25 believe I provided a complete and thorough	1 Again, I don't know all the arguments 2 that have been presented in this case and don't 3 know whether this has been addressed in other 4 areas. 5 I provided a fulsome response to 6 Dr. Cooper's theories, and I'm happy to discuss 7 those with you today. 8 Q. Can you identify any teaching away 9 from the claimed invention in the suit from the 10 literature or prior art? 11 MS. RAYMOND: Objection. Form. 12 A. I'm not sure what specifically you're 13 referring to. If you can point me to places in 14 my report where I talk about teaching away, I'd 15 be happy to refresh my memory. 16 Q. Okay. 17 If you turn to paragraph 23. 18 A. Sure. 19 Q. And you list as one of the objective 20 indicia of nonobviousness that the board must 21 consider is whether there's teaching away. And 22 then you wrote, "(...e.g., literature telling 23 persons of skill not to do something that would 24 be required by the claims),..." 25 Do you see that?
Page 27	Page 29
1 analysis of Dr. Cooper's theories. And I 2 believe what I have here is a fulsome response. 3 And I'm happy to discuss what I included in my 4 report. 5 Q. Can you answer my question directly? 6 A. I believe I've answered your question 7 multiple times. 8 I was asked to respond to 9 Dr. Cooper's assertions about the '918 [sic] 10 patent and I believe -- or, sorry, '981, I may 11 have said '918 previously too -- the '918 [sic] 12 patent and I believe I provided a fulsome 13 response. 14 Q. Why did you include in your report 15 that objective indicia was part of the 16 obviousness analysis and that the board must 17 consider it if you didn't include any such 18 analysis in your report? 19 A. In the section on obviousness, I was 20 trying to include as complete an understanding 21 as necessary -- as complete an understanding as 22 possible, given the fact that I'm not an 23 attorney or a licensed patent agent. And so I 24 believe this is a reasonable summary of what the 25 criteria are.	1 A. Yes, I do. 2 Q. Can you identify any teaching away? 3 A. I don't recall. If you can point me 4 to places in my report where I discuss teaching 5 away, I'm happy to refresh my memory. 6 Q. Do you have an opinion here one way 7 or the other whether there is teaching away as 8 an objective indicia of nonobviousness? 9 MS. RAYMOND: Objection. Form. 10 A. I don't recall rendering such an 11 opinion. If you can point me to places in my 12 report where I offered such an opinion, I'd be 13 happy to refresh my memory. 14 Q. Did you investigate whether there was 15 a teaching away from the claimed inventions? 16 MS. RAYMOND: Objection. Form. 17 A. I was asked to respond to 18 Dr. Cooper's assertions about obviousness. To 19 the extent that Dr. Cooper rendered or offered 20 any opinions, I responded to those regarding 21 teaching away. And if it does appear in my 22 report, if you'd point me to them, I'd be happy 23 to discuss them with you. 24 Q. Do you remember investigating whether 25 there was the objective indicia of teaching away

Page 30	Page 32
1 in the prior art from the claimed inventions? 2 MS. RAYMOND: Objection. 3 Q. Did you investigate that from your -- 4 based on your memory? 5 MS. RAYMOND: Objection to form. 6 A. Sitting here today, what I was asked 7 to do was to respond to Dr. Cooper's arguments. 8 And so I don't recall offering such opinions in 9 my report. If you'd like to point me to those, 10 I'd be happy to refresh my memory. 11 Q. If you turn to paragraph 25, please. 12 A. All right. 13 Q. In terms of the skill level in the 14 art, you addressed that in paragraph 25; is that 15 correct? 16 A. Twenty-five and 26. 17 Q. And you formed your analysis, 18 basically, under the skill level in the art 19 identified by Dr. Cooper and the skill level in 20 the art identified by you; is that correct? 21 Well, let me make it easier. Do you 22 see at the end, you say, "My opinions would not 23 change if I applied that definition of a person 24 of skill"? 25 Do you see that?	1 either my definition or Dr. Cooper's definition 2 and also that I had supervised people as of 2009 3 who had the relevant opinion of either one. 4 In terms of overall knowledge and 5 understanding, I didn't see a great difference. 6 And so essentially at the end of the day, I've 7 applied both definitions. And the opinions I 8 set forth are consistent with those. 9 Q. You believe that you qualify as a 10 person of skill in the art in 2009 under 11 Dr. Cooper's definition; is that correct? 12 A. So I took the opportunity to look 13 back at Dr. Cooper's multiple definitions. So 14 he lists people with both a master's degree or 15 Ph.D., as well as people with -- individuals 16 with a bachelor's degree, periods of experience, 17 familiarity with a variety of different 18 techniques. And then also I looked back at my 19 definition, and as I state in paragraph 6, well 20 before August 2009, my level of the skill in the 21 art was at least that of a person of ordinary 22 skill in the art. So, yes, I do. 23 Q. Where the answer is just "yes," you 24 don't -- you know, please try to be as concise 25 as you can. You don't need to give long, you
Page 31	Page 33
1 A. Yes, I do. 2 Q. Okay. 3 And there, you're referring to 4 Dr. Cooper's definition; is that right? 5 A. So -- 6 Q. I'm just asking. There will be a 7 broader question in a minute. But I'm just 8 asking you now, when you say, "My opinions would 9 not change if I applied that definition of a 10 person of skill," you're referring to 11 Dr. Cooper's opinion? 12 A. Here, specifically, when I say "that 13 definition," I'm applying to -- I'm referring to 14 Dr. Cooper's definition. 15 Q. Okay. All right. Thank you. 16 And in order to determine that there 17 would be no difference, you performed the 18 obviousness analysis both under -- from the 19 vantage point of your level of skill in the art 20 and Dr. Cooper's; is that correct? 21 A. So I initially applied my definition. 22 I also looked at Dr. Cooper's definition. 23 Recognizing that as of 2009, I had at least the 24 skill and experience and training of a person of 25 ordinary skill in the art that would match	1 know, just verbiage if the answer is "yes." 2 In paragraph 26, you state that you 3 would have qualified as a person of skill in the 4 art under Dr. Cooper's definition in 2009; is 5 that right? 6 A. Yes. I would have qualified under 7 both my and Dr. Cooper's definition. 8 Q. And before August 2009, were you 9 familiar with the tools, method and techniques 10 listed as 1 through 6 in your report on page 10? 11 A. So what's listed as 1 through 6 are a 12 part of Dr. Cooper's criteria, and I was 13 familiar with those as of August 2009. 14 Q. And what was your knowledge of 15 polynucleotide tagging as of before August 2009? 16 A. Would you like a comprehensive review 17 of my work prior to 2009. 18 Q. If you could just describe what you 19 knew about polynucleotide tagging as a person 20 skilled in the art as of August 2009 time 21 period. 22 MS. RAYMOND: Objection to form. 23 A. My Ph.D. was in theoretical physics. 24 I worked for two years as a postdoctoral fellow 25 in physics.

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1 In 1992, I received a five-year 2 fellowship to work on the Human Genome Project. 3 I began my career at the Salk Institute in 4 San Diego. At the Salk, I went into the lab and 5 threw myself into learning all the laboratory 6 techniques, starting with things like PCR, so 7 that's an amplification technology; DNA 8 sequencing; ligation and primer detection, the 9 use of tags. And there are a variety of 10 different types of tags that one can use to 11 overcome amplification bias that would include 12 things like universal primers or single primers, 13 ways of tagging different polynucleotides, and 14 we can discuss about radioactive tags, 15 fluorescent tags, other tags like biotin, mass 16 tags that people have used. I'm not providing 17 an exhaustive list. 18 And then in the early 2000s, people 19 were very interested in analyzing, while I was 20 at the Dana-Farber Cancer Institute, circulating 21 tumor cells and began to become familiar with 22 techniques that -- 23 (Reporter clarification.) 24 A. At the Dana-Farber Cancer Institute, 25 people were interested in analyzing circulating	1 Q. When you refer to this zip coding, 2 was the molecular barcoding at Stanford in the 3 1990s, was that polynucleotide barcoding? 4 MS. RAYMOND: Objection to form. 5 A. It would depend on how you describe 6 polynucleotide barcoding or polynucleotide 7 tagging. The tags were polynucleotides. 8 Q. The tags themselves or they were part 9 of polynucleotides? 10 MS. RAYMOND: Objection to form. 11 A. It's going to depend on how you 12 define polynucleotide tagging. They were 13 polynucleotides that were used as tags. 14 Q. Did you have any awareness of 15 polynucleotide tagging in which random barcodes 16 were added to polynucleotides prior to August of 17 2009? 18 MS. RAYMOND: Objection to form. 19 A. So would you repeat the question, 20 please? 21 Q. Yes. 22 Were you aware of polynucleotide 23 tagging using random barcodes added to 24 polynucleotides prior to August 2009? 25 MS. RAYMOND: Objection to form.
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1 tumor cells. And so I became familiar with 2 methods that had been developed in the early 3 2000s for doing that. 4 So my background with all of this 5 really extends back to the start of my career in 6 the biological sciences in 1992. And I can 7 probably even come up with examples before that. 8 Q. Did I have any experience with 9 molecular barcoding as a means for 10 polynucleotide tagging prior to August 2009, you 11 personally? 12 MS. RAYMOND: Objection to form. 13 A. So one would have to look at how one 14 would describe molecular barcoding. When I was 15 at the Stanford Human Genome Center in the late 16 1990s, Ron Davis and some of his post-docs and 17 students had been developing what they called, I 18 believe, a zip code array in which they were 19 tagging yeast cells to track those yeast cells. 20 And those tags represented what would call a 21 molecular barcode. 22 I believe there's literature that 23 exists describing that and so -- and describing 24 other approaches. So I'm familiar with 25 molecular barcoding as a type of tagging.	1 A. So in paragraph 31 of my report, I 2 actually respond to an argument Dr. Cooper makes 3 about claim 1 of the '918 [sic] -- or '981. I 4 keep on saying '918 [sic], and I apologize -- 5 '981 patent that I've called out in a box on 6 page 15. And that passage in the patent that 7 Dr. Cooper cites relates to, and I'm quoting my 8 report, "...a technique known as 'multiplex' 9 sequencing in which individual DNA samples (from 10 distinct bulk sources) are labeled with 11 sample-specific molecular barcodes (or 'sample 12 bar codes') during library construction, 13 multiplex sample libraries are pooled and 14 sequenced (referred to as 'multiplex 15 sequencing') and the resulting data 16 'demultiplexed' to group sample-specific 17 sequences based on their bar codes." 18 So there are barcoding techniques 19 that have been used for multiplex sequencing, 20 some of those may have involved I believe you 21 referred to as random barcodes, but the use of 22 barcodes from multiplex sequencing was well 23 known in the art before 2009. 24 Q. And in terms of what you knew, how 25 could you accomplish polynucleotide tagging with

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1 barcodes prior to August 2009, what were the 2 methods -- 3 A. There were a variety -- 4 Q. -- that you knew of? 5 A. There were a variety of different 6 methods that people used. This type of 7 multiplex tagging that I'm referring to here in 8 paragraph 31 was largely accomplished in the 9 library preparation steps from Illumina since a 10 lot of the sequencing that was done at the time 11 was on Illumina sequencers. But each of the 12 technology companies, at least the major 13 players, Illumina Applied Biosystems, who had 14 the solid sequencer. I believe the 454 was 15 still providing sequencing technology. To the 16 best of my recollection, they all had multiplex 17 sequencing tech capabilities that relied on 18 sample barcodes. And there were a variety of 19 different ways that those could be introduced. 20 They could include -- and it would 21 depend on the application and how they were 22 used. They could be introduced by PCR. They 23 could be introduced in a variety of different 24 ways. 25 Q. Other than PCR, what other ways were	1 those methods that are included in my report. 2 Q. Other than PCR, can you, sitting here 3 now, identify any other known technique as of 4 August 2009 for polynucleotide barcoding? 5 MS. RAYMOND: Objection to form and 6 scope. 7 A. I mentioned earlier the work that Ron 8 Davis and his colleagues had done in tagging 9 yeast, and they used molecular recombination 10 yeast. 11 So there were a variety of different 12 ways that people could perform this. It would 13 depend on the application and the particular 14 goals. Those that are relevant to responding to 15 Dr. Cooper's arguments are presented in my 16 report. 17 Q. The second technique that you say you 18 were familiar with as of August of 2009 was 19 amplification. 20 What did you know about amplification 21 as a tool for nucleic acid analysis in August 22 2009? 23 MS. RAYMOND: Objection to form and 24 scope. 25 A. By August of 2009, I personally had
Page 39	Page 41
1 there that you were aware of prior to August 2 2009 to add barcodes to polynucleotides? 3 MS. RAYMOND: Objection to form. 4 A. I would have to look back and refresh 5 my memory as to the breadth and scope of those. 6 I don't believe that I needed to really look 7 back at all the possible ways of introducing 8 polynucleotides because Dr. Cooper doesn't 9 provide an extensive list of different ways 10 polynucleotide tags would be introduced. 11 Q. My question was in terms of what you 12 knew yourself personally in 2009 regarding 13 polynucleotide tagging. I understand you're 14 saying you were familiar with that at that time. 15 My question is, were you familiar 16 with ways other than PCR, you personally? 17 MS. RAYMOND: Objection to form. 18 A. So the '918 [sic] patent describes -- 19 sorry, the Linnarsson patent, which we 20 discussed, provides at least one way of 21 introducing those barcodes, a type of molecular 22 barcode through their template switching oligos. 23 I mean, there's a laundry list of different 24 methods, and I couldn't provide a comprehensive 25 list sitting here today. I'm happy to discuss	1 probably done tens of thousands, if not hundreds 2 of thousands of PCR amplifications. So I'm 3 familiar with many different PCR techniques and 4 variations; isothermal amplification, 5 amplification -- a variety of different 6 amplification techniques like MDA. I can't tell 7 you exactly when all of these were invented or 8 presented. There are a large number of ways, 9 rolling circle amplification, padlock probes, 10 all of which can be used for different aspects 11 of DNA analysis and in different circumstances 12 and different situations. 13 I amplified many things for DNA 14 sequencing. I amplified them for analysis on 15 agarose gels. You know, there are 16 polyacrylamide gels. You know, there are many, 17 many, many different techniques that have been 18 developed for DNA amplification. 19 Q. Did you personally have experience as 20 of August 2009 with amplification of RNA? 21 A. RNA typically is not directly 22 amplified. RNA is first converted to something 23 called cDNA. It uses an enzyme from 24 retroviruses called reverse transcriptase, which 25 copies the RNA, typically messenger RNA, into

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1 what's called cDNA, complementary DNA, and 2 that's typically what's amplified. 3 Q. Did you personally perform techniques 4 or have them performed under your supervision of 5 converting mRNA to cDNA and then amplifying 6 cDNA? 7 A. Yes. I launched a whole program in 8 gene expression analysis when I was at the 9 Institute for Genomic Research. I used to teach 10 workshops every summer at the Jackson Laboratory 11 in Maine where I teach people how to do that. 12 And I oversaw a large gene expression program at 13 TIGR. And then when I moved to Dana-Farber, in 14 March of 2005, transitioned the DNA array-based 15 analysis of gene expression to RNA sequencing. 16 So, yes, I mean, my experience by that time was 17 fairly extensive. 18 Q. As of August 2009, were you familiar 19 with molecular biology techniques such as those 20 described in Linnarsson -- 21 MS. RAYMOND: Objection to form. 22 Q. -- where there's mRNA and then you 23 convert that to cDNA? 24 A. By 2009, I was very familiar with 25 techniques for analyzing gene expression,	1 discussion of the Linnarsson patent. 2 In Linnarsson, one of the figures 3 that Dr. Cooper presents in his report and that 4 I discussed fairly extensively is Figure 11 in 5 the Linnarsson patent. 6 Linnarsson introduces in Step C of 7 his process two regions -- or in Step B they're 8 introduced and then tracked through -- that are 9 called PR. And these represent universal 10 primers. And he uses a single primer extension 11 to do his analysis. 12 So I was at least familiar with these 13 types of techniques, as well as others. 14 Q. And please describe those others. 15 A. It would be a fairly extensive 16 catalogue, and, yeah, I'm not prepared to give 17 you the entire list today. 18 Q. Other than the one that Dr. Cooper 19 brought to your attention, what other use of 20 tags to overcome amplification bias were you 21 familiar with as the standard techniques prior 22 to August 2009? 23 MS. RAYMOND: Objection. Scope. 24 A. So I don't believe I discussed any of 25 those in my report, and so I couldn't provide
Page 43	Page 45
1 including the creation of cDNAs for a variety of 2 different applications. 3 At TIGR, The Institute for Genomic 4 Research, I oversaw a project before arrays that 5 included sequencing, what we called ESTs, or 6 expressed sequence tags, that involved 7 converting RNA to DNA and then sequencing them. 8 I worked with a large consortium 9 centered -- really centered at the Riken 10 Laboratory in Japan doing full-length sequencing 11 in mouse. So I've had extensive experience with 12 analyzing -- full-length RNA sequencing. So 13 I've had extensive experience with reverse 14 transcription and cDNA preparation and analysis. 15 Q. One of the techniques you say you 16 were familiar with as of August of 2009 was the 17 use of tags to overcome amplification bias. 18 Please describe what experience 19 you've had with that before August of 2009. 20 A. So there are many different ways of 21 using -- potentially using tags to overcome 22 amplification bias. One of the simplest is the 23 use -- the introduction and use of what one 24 could call universal primers for PCR. And 25 that's something since -- this is relevant to my	1 you with a comprehensive catalogue sitting here 2 today. 3 Q. Yeah, I'm not asking for a 4 comprehensive catalogue. Just examples is fine. 5 MS. RAYMOND: Objection. Scope. 6 A. I'd have to think back to the 7 relevant time frame as of 2009. 8 I'm not prepared to do that today. 9 Q. So other than what Dr. Cooper brought 10 to your attention in his report, you're not -- 11 you, as of August 2009, you can't say you're 12 aware of any other tags used to overcome 13 amplification bias with polynucleotides? 14 MS. RAYMOND: Objection. Form. 15 Scope. 16 A. So I'm sorry, I'm looking for -- 17 there's a place that I recall in my report 18 quoting Linnarsson, where Linnarsson talks about 19 the use of primers to reduce bias in PCR. And I 20 forget the adjective that Linnarsson uses to 21 describe his primers. It may have been single 22 primers, single universal primers, I don't 23 recall exactly, as a way of reducing bias in 24 PCR. 25 Depending on the application, there

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1 are other ways to reduce bias in PCR in 2 amplification. And I don't provide a 3 comprehensive list of those here. Sitting here 4 today, I'm not prepared to provide a list since 5 that list wasn't required for me to respond to 6 Dr. Cooper's arguments about the obviousness of 7 the '981 patent. 8 Q. In terms of your opinion that, as of 9 August 2009, you were familiar with the use of 10 tags to overcome amplification bias, you 11 supported that by stating that you were familiar 12 with the use of universal primers for that. 13 Is there any other support that you 14 have for that opinion? 15 A. I wouldn't say that's an opinion. I 16 would say that's a fact. And I talk about the 17 use of -- again, there's some place in this 18 report, and I'm happy to read through it and 19 find it if you'd like. If you can point me to 20 the place where I refer to that or provide me 21 with a searchable copy, I'm happy to find it. 22 Q. Sure. Turn to paragraph 26, please. 23 A. Sure. 24 Q. You state that you are qualified as a 25 person of skill in the art as of August 20,	1 tag. And the use of universal primers is one 2 way, and it's discussed in Linnarsson. I'm 3 happy to read through my report in Linnarsson, 4 if you'd like, to find where Linnarsson 5 discusses -- or I discuss Linnarsson's 6 presentation of producing amplification bias. 7 Q. When you say that you were familiar 8 in August of 2009 of the use of tags to overcome 9 amplification bias, do you consider primers to 10 be tags? 11 MS. RAYMOND: Objection. Form. 12 A. It would depend on the context in 13 which it's used. 14 Q. In that way, where Dr. Cooper says 15 the use of tags to overcome amplification bias 16 was a known technique for people of ordinary 17 skill in the art in August 2009 and you say you 18 had that competency, my question to you is, in 19 that context, is a primer a tag? 20 MS. RAYMOND: Objection to form. 21 A. I don't -- I can't tell you what 22 Dr. Cooper was thinking about when he wrote 23 that. If you provide me with his report or show 24 me where he provides more detail as to what he 25 describes as tags, I would be happy to refresh
Page 47	Page 49
1 2009, under Dr. Cooper's definition. 2 Do you see that? 3 A. Yes, I do. 4 Q. Okay. 5 And do you recall earlier in the 6 deposition, you said that, in that regard, you 7 would have been familiar with tools, methods and 8 techniques identified by Dr. Cooper listed as 1 9 through 6 as of August of 2009? 10 A. Yes, I do. 11 Q. And one of the things that you're 12 saying now that you would have been familiar 13 with as of August 2009 was the use of universal 14 primers to address amplification bias, right? 15 It's Item 3. 16 A. He says use of tags to overcome 17 amplification bias, one type of tag could be a 18 primer. And so that's at least one technique 19 that I can point you to. And I believe that one 20 is relevant to the discussion provided in my 21 report. 22 Q. As of August 2009, how did you 23 understand primers could be used as a tag to 24 overcome amplification bias? 25 A. Some people refer to primers as a	1 my memory of what Dr. Cooper is arguing. 2 I will tell you that primers are one 3 type of tag that is sometimes referred to in the 4 literature. And so that may or may not have 5 been what Dr. Cooper is referring to. 6 I don't believe Dr. Cooper presents 7 more detail than what's presented here. So as 8 one example that I've provided, the use of tags 9 as a way of reducing bias in amplification is 10 something that's discussed in Linnarsson. And 11 so sitting here today, that's what I recall. I 12 haven't done a comprehensive analysis to list 13 all the different methods because it's not 14 relevant to the opinions offered in my report. 15 Q. In August 2009, were you familiar 16 with the techniques described in Linnarsson to 17 use tags to overcome amplification bias, you 18 personally? 19 A. So Linnarsson's -- I don't know if 20 Linnarsson refers directly to the -- I don't 21 know if -- I'm not sure exactly how Linnarsson 22 describes different types of tags. Linnarsson 23 describes a barcode, which is one type of tag, 24 which can be used to reduce bias. 25 Linnarsson also describes the use

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1 of -- I think he refers to them as universal. I 2 think he actually talks about single primer PCR, 3 which would be a type of universal PCR, as a way 4 of reducing bias. 5 So at least those two are methods 6 that are discussed in Linnarsson that I'm 7 familiar with. 8 Q. Would you have been familiar with 9 them -- are you saying you were familiar with 10 them in August of 2009? 11 (Clarification by the reporter.) 12 Q. Let me ask the full question. 13 As of August 2009, were you familiar 14 with the two techniques you just described in 15 Linnarsson for the use of tags to overcome 16 amplification bias, you personally? 17 A. So you're asking a complex question 18 because Linnarsson describes a multistep 19 multiparameter process. So to the extent that 20 your question is limited to single primer PCR or 21 universal primer PCR, and Linnarsson, I believe 22 -- I believe he refers to them as barcodes, 23 sample barcodes. To the extent that Linnarsson 24 is using both of those and we limit our 25 discussion to those two elements, I was very	1 approaches and different techniques. 2 Q. What single-cell analysis were you 3 familiar with as of August of 2009? 4 A. I'd have to think back and look at 5 all the different methods that had been proposed 6 and had been used. I don't recall all of them. 7 I do recall being involved in projects before 8 2009 that involved the analysis of circulating 9 tumor cells. I also was involved in a process 10 -- in a project that looked at -- it was one 11 started by one of my graduate students in which 12 we looked at the distribution of RNA molecules 13 in individual cells to assert that they followed 14 the Poisson distribution across populations. 15 And we did a series of directed PCR experiments 16 doing limited -- limiting dilutions of 17 individual -- I think they were human cells, 18 they may have been yeast cells, I don't recall 19 -- looking at a subset of specific molecules and 20 their expression levels. 21 So at least, yeah, in a variety of 22 different applications, I was familiar with the 23 analysis of single cells. Whether or not that 24 would qualify as single-cell analysis would 25 depend on the context.
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1 familiar with those as of 2009. 2 Q. Where did you gain that knowledge? 3 A. I've been working in the field since 4 -- directly in the field since I began my work 5 in molecular biology at the Salk Institute in 6 September of 1992. So at the Salk, at Stanford, 7 at the Institute for Genomic Research, and by 8 2009, at the Dana-Farber Cancer Institute. 9 MS. RAYMOND: I think we've been 10 going for more than an hour at this point. 11 I don't know if the witness needs a break. 12 THE WITNESS: We should give the 13 court reporter a break. I'm happy to sit 14 and go for a long time. 15 MR. REINES: If we can go to the 16 bottom of the hour, if that works? 17 THE WITNESS: Is that all right with 18 you? I'm more concerned about you than me 19 right now. 20 BY MR. REINES: 21 Q. Are you saying August of 2009, you 22 were familiar with single-cell analysis, you, 23 Dr. Quackenbush? 24 A. So people use the phrase single-cell 25 analysis to refer to a variety of different	1 Q. And in terms of your statement that, 2 as of August 2009, you were familiar with 3 single-cell analysis like a person of ordinary 4 skill in the art as set forth here, do you 5 believe in that sense that you were familiar 6 with single-cell analysis? 7 A. So I'm not sure what Dr. Cooper 8 specifically is referring to here. Again, he 9 doesn't provide a fulsome definition of what he 10 means by single-cell analysis. 11 There are a variety of different ways 12 of examining this, and we'd have to look at them 13 in context. If we limit it to the analysis of a 14 single cell -- well, we'd have to look at it in 15 context. 16 But by August of 2009, I was involved 17 in analysis of single cells, and my familiarity 18 of that in the literature was sufficient to be 19 able to read Linnarsson, to read Dr. Cooper's 20 arguments about Linnarsson and to render the 21 opinions set forth in my report. 22 Q. As of August 2009, at Dana-Farber, 23 were you -- was your lab interested in pursuing 24 single-cell analysis as a research area? 25 MS. RAYMOND: Objection to form.

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1 A. So I'm not sure exactly what you mean 2 by "single-cell analysis" since it's used in 3 different ways in different contexts. 4 We were very interested in the 5 analysis of particular mutations that occurred 6 in circulating tumor cells and also in the 7 analysis of gene expression in circulating tumor 8 cells. But the analysis, the approaches and the 9 techniques depended on the particular 10 experimental question they were trying to 11 address. 12 I was certainly familiar enough with 13 the methods in the literature to render the 14 opinions set forth in my report. 15 Q. Prior to August 2009, was your lab at 16 Dana-Farber interested in being able to trace 17 mRNA expression to particular cells within a 18 sample? Was that something that was on your 19 radar? 20 A. So, again, I'm not sure I fully 21 understand your question in what context you're 22 asking it. I can tell you, that as of 2009, we 23 were very interested in the analysis of 24 circulating tumor cells, and some of that may 25 have involved trying to analyze the expression	1 the analysis of circulating tumor cells. I do 2 recall that in 2009, my group received funding 3 to get the first Illumina sequencer at 4 Dana-Farber, and so there was a great deal of 5 interest in a wide variety of different 6 applications. But reviewing my work at the time 7 and the extent of it was not necessary to 8 respond to Dr. Cooper's arguments and so I can't 9 provide you with detailed answer sitting here 10 today. 11 Q. Who were the groups that you were 12 working with that were very interested in the 13 analysis of a circulating tumor cells at the 14 single-cell level? 15 MS. RAYMOND: Objection. Scope. 16 A. I am not very good at remembering 17 names, unfortunately. And I recall a number of 18 different individuals I worked with at the 19 Dana-Farber Cancer Institute, Brigham and 20 Women's Hospital and Massachusetts General 21 Hospital at a minimum, but I couldn't tell you 22 the individuals sitting here today. It's not 23 something I reviewed in preparing for my 24 testimony. 25 Q. So you can't identify any individual
Page 55	Page 57
1 in those individual tumor cells. 2 Q. When you say "may have," was it or 3 you don't know? 4 A. I don't recall the exact work we were 5 doing with circulating tumor cells. That's not 6 something that I looked back to refresh my 7 memory in preparing this report. 8 Q. What was the state of the art of 9 single-cell analysis in August of 2009? 10 MS. RAYMOND: Objection to form. 11 A. So that's a rather broad question. 12 It would depend on the context in which you were 13 going to describe or discuss single-cell 14 analysis. I didn't review all of the existing 15 technologies and techniques in preparing this 16 report. It wasn't necessary to respond to 17 Dr. Cooper's arguments. 18 Q. In terms of your lab at Dana-Farber, 19 what was your interest in single-cell analysis 20 at that time? 21 MS. RAYMOND: Objection to form. 22 A. So that was 15 years ago, and I don't 23 recall exactly all the work that we were doing 24 at that time. I do recall that I was working 25 with some groups that were very interested in	1 or group? 2 MS. RAYMOND: Objection to form. 3 Scope. 4 A. Sitting here today, I can't tell you. 5 That's not something I reviewed in preparation 6 for in either preparing my report or in 7 preparation for my testimony today. 8 Q. As of August 2009, you were familiar 9 with ligation and primer extension as 10 techniques; is that correct? 11 A. Broadly speaking, yes. 12 Q. As of August 2009, were you familiar 13 with the use of ligation for polynucleotide 14 tagging? 15 MS. RAYMOND: Objection to form. 16 A. So as of 2009, I personally performed 17 a number of ligation experiments, both what we 18 refer to as sticky-ended and blunt-ended 19 ligation. A number of those introduced a 20 variety of different tags, including sequencing 21 tags such as sequencing primers. 22 I was also familiar with ligation in 23 the context of sequencing instruments like the 24 Applied Biosystems SOLiD, which performed 25 sequencing by ligation, as well as other

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1 applications. 2 Q. As of August 2009, were you familiar 3 with the use of ligation for added tags to 4 overcome amplification bias? 5 MS. RAYMOND: Objection to form. 6 A. So I'm not sure what particular 7 approaches you're referring to with regard to 8 this combination of techniques that Dr. Cooper 9 lists. I don't believe Dr. Cooper provides 10 explicit examples of those combinations. 11 To the extent that at a very minimum 12 one could introduce sequencing primers and one 13 could on call a sequencing primer a particular 14 tag, I was familiar with those approaches. I 15 was also familiar with the introduction of 16 amplification primers through ligation. And the 17 use of universal primers is one way of 18 overcoming amplification bias. 19 "Overcoming" is a challenging term to 20 use. Of addressing amplification bias would 21 with probably be a better way of describing what 22 Dr. Cooper is referring to. 23 Q. I just need to ask that again because 24 I'm not sure I tracked your response, if you had 25 a specific one.	1 Scope. 2 A. So I don't believe I rendered any 3 opinion about that in response to Dr. Cooper's 4 arguments. If you can point me to places where 5 I rendered opinions about that, I'd be happy to 6 refresh my memory. 7 As of 2009, I was familiar with 8 ligation. I was familiar with Illumina 9 sequencing. There may or may not have been 10 applications of and other sequencing platforms. 11 Earlier we discussed multiplex 12 sequencing using sample barcodes to deconvolute 13 the source of different sequences, and I believe 14 that some of the techniques that were in use at 15 the time involved use of ligation to introduce a 16 variety of different tags on universal primers, 17 potentially multiplex barcodes and potentially 18 others. 19 Q. When you say that as of August of 20 2009, you were aware of techniques to introduce 21 a variety of different tags to polynucleotides, 22 you say potentially multiplex barcodes, were you 23 aware of that or not as of August 2009? 24 MS. RAYMOND: Objection to form. 25 Q. Without using ligation.
Page 59	Page 61
1 What did you personally know of as 2 techniques for using ligation to introduce 3 barcodes for addressing amplification bias? 4 MS. RAYMOND: Objection to form. 5 A. So Dr. Cooper doesn't refer to tags 6 -- to barcodes. He says use of tags. One of 7 the types of tags, sitting here today, that I 8 can tell you that we used was universal primers 9 and that we introduced universal primers in a 10 variety of different ways, including through 11 ligation, and that the use of universal primers 12 is one way of reducing amplification bias. 13 Q. In August of 2009, you were not aware 14 of any way to use ligation to add barcodes to 15 polynucleotides; is that correct? 16 MS. RAYMOND: Objection to form. 17 A. I don't believe I said that. 18 Q. Is it true? 19 A. Sorry, can you repeat the question? 20 Q. Yes. 21 As of August of 2009, were you 22 familiar with techniques in the field for using 23 ligation to add molecular barcodes to 24 polynucleotides? 25 MS. RAYMOND: Objection. Form.	1 MS. RAYMOND: Objection. 2 A. So sitting here today, I don't recall 3 discussing that because I don't think it was 4 necessary to respond to Dr. Cooper's arguments. 5 I was familiar with ligation as a technique 6 dating back to the 19- -- my personal experience 7 with it dating back to the 1990s, both blunt end 8 and sticky ligation. And I believe that as of 9 2009, there were protocols for high throughput 10 sequencing, such as that used by Illumina and 11 Applied Biosystems, Helicos Biosystems, 454, 12 other companies for doing multiplex sequencing 13 that used ligation as a way of introducing 14 sample-specific barcodes for multiplex 15 sequencing and demultiplex. 16 MR. REINES: Why don't we take that 17 break. 18 VIDEOGRAPHER: We're off the record 19 at 10:34. This ends is Media Unit No. 1. 20 (Recess.) 21 VIDEOGRAPHER: We're on the record at 22 10:49. This begins Media Unit 2 in the 23 deposition of John Quackenbush, Ph.D. 24 BY MR. REINES: 25 Q. Going back to your skilled in the art

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1 opinion on paragraph 25. 2 Do you have that in front of you? 3 A. Yes, I do. 4 Q. In the first sentence, you say, "I've 5 been asked to assume that persons skilled in the 6 art..." and then you go on to have a definition. 7 Do you see that? 8 A. Yes. 9 Q. And when you say "assume," is that an 10 opinion that you reach based on your analysis or 11 is that just an assumption that you've been 12 asked to make by counsel? 13 A. So as I mentioned earlier, I prepared 14 this report collaborating with the attorneys 15 from Groombridge representing 10x. And in our 16 discussions about the skill level of a person of 17 ordinary skill in the art, this was what, in our 18 discussions, we believed to be appropriate. And 19 so I was asked to make the assumptions that 20 that's what background a person of ordinary 21 skill in the art would have. 22 Q. Do you have an affirmative opinion 23 that this is, in fact, the right definition or 24 are you just assuming it for purposes of this 25 proceeding?	1 describes the use of a multiplex identifier. 2 And I don't have the patent in front of me, but 3 in paragraph 32, I break out claim 1 of the 4 patent as broken down by Dr. Cooper. And the 5 patent describes the use of what are called 6 multiplex identifiers or MIDs. And they have 7 two tag sequences. The first tag sequence is 8 associated with the single cell from which the 9 sample polynucleotide is derived. And the 10 second sequence -- tag sequence distinguishing 11 the sample polynucleotides from other sample 12 polynucleotides derive from the same cell. 13 So in this context, the cell-specific 14 tag is the part of that MID that's used to 15 identify the source of molecules and trace them 16 back to individual cells. 17 Q. And the second part of that is the 18 polynucleotide-specific tags that you read into 19 the record? 20 A. Yes. The second tag sequence 21 distinguishing the sample polynucleotide from 22 others. 23 Q. Down further in paragraph 28, you 24 state, "...to accomplish'..." -- you quote, 25 excuse me, the '981 patent. And I'm happy to
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1 A. I believe this is an appropriate 2 definition. But as I wrote, I could either 3 assume my opinion or Dr. Cooper's opinion about 4 what a person of ordinary skill in the art would 5 have in their background, and my opinions 6 overall about the validity of the '981 patent 7 would not change. 8 Q. How come you didn't include an 9 opinion contesting Dr. Cooper's definition of 10 the skill level in the art? 11 A. It wasn't necessary because as I 12 stated here in the bottom, my opinions would not 13 change if I applied either Dr. Cooper's 14 definition or my definition. 15 Q. If you turn to paragraph 28. 16 A. All right. 17 Q. You refer in paragraph 28, about five 18 lines down, to a cell-specific tag. 19 Do you see that? 20 A. Yes, I do. 21 Q. And do you know what a cell-specific 22 tag is? 23 A. So in the context of the '918 [sic] 24 patent -- sorry, I keep saying '918 -- '981. In 25 the context of the '981 patent, the patent	1 give you that since you mentioned that. 2 A. Thank you. 3 (Exhibit 1001 was produced.) 4 Q. Let me show you Exhibit 1001, which 5 is the '981 patent. 6 A. Thank you. 7 Q. But you cite this patent to state, 8 "...to accomplish such molecular tagging the 9 number of distinct MID tags to be used should be 10 many times greater than the number of molecules 11 to be analyzed." 12 Do you see that? 13 A. Yes, I do. 14 Q. Did you know, as of August of 2009, 15 that for cell-specific and 16 polynucleotide-specific tagging, you would need 17 tag -- the number of distinct tags would have to 18 be many times greater than the number of 19 molecules to be analyzed? 20 A. So I'm not sure I understand your 21 question, but it's a fairly-simple analysis that 22 one has to do. So when we're talking about the 23 number of distinct tags -- 24 Q. Right. 25 A. -- being greater than the number of

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1 molecules to be analyzed, I can look back at 2 column 22 in the patent, but I believe this is 3 referring to the number of polynucleotides or 4 number of molecules in each individual cell. 5 If each molecule is to be uniquely 6 tagged within each individual cell, then that 7 second part of the tag -- so every cell is going 8 to have a first sequence associated with that 9 cell, which is going to be the same, and then 10 the second part is going to be variable. And 11 that's going to be useful for identifying the 12 individual molecules. 13 And it's a simple statistical 14 analysis that one has to do to realize that if 15 you want each molecule to be uniquely tagged, 16 the number of tags has to be greater than the 17 number of molecules. 18 It's, basically, the same statistical 19 problem as being in a party and trying to 20 identify unique birthdays. If you have more 21 than about 30 people, there's a greater than 50 22 percent chance that two individuals will have 23 the same birthday, even though there are 365 24 days and there's only 30 people. 25 Q. In paragraphs 29 and 30, you refer to	1 also now become -- HER2 has become an important 2 marker in colon cancer. There's a drug called 3 Herceptin that specifically targets HER2 4 amplification in breast cancer. 5 And as of 2005, I published a number 6 of papers, at least one that I can recall 7 immediately, that provided a molecular 8 characterization of breast cancer subtypes using 9 HER2 expression explicitly. 10 Q. In terms of HER2 expression analysis, 11 did you at Dana-Farber use bulk analysis or did 12 you use single-cell analysis? 13 A. Most of the analysis that we've done 14 used bulk tissue analysis because those were 15 primarily the clinical assays being performed at 16 the time. 17 Q. Prior to August of 2009, were you 18 aware of the benefits of performing a single 19 cell analysis for the HER2 gene as compared to 20 the bulk analysis that you seem to be using? 21 MS. RAYMOND: Objection. Scope. 22 A. So I don't recall performing that 23 analysis. If you asked me about the potential 24 value of being able to do this with an 25 individual cell or with a collection of cells,
Page 67	Page 69
1 this HER2 gene. 2 Do you see that? 3 A. Yes, I do. 4 Q. Do you know whether the claimed 5 methods of the '981 patent have ever been used 6 clinically? 7 A. That's not an analysis that I 8 performed, and so sitting here today, I can't 9 tell you whether or not they have been used 10 clinically. 11 Q. And in terms of the HER2 gene that 12 you referred to in paragraph 29 and 30, that's 13 just something you used as an example or did you 14 get that from the patent or something else? 15 A. So this is an example that comes from 16 my experience, commonly referred to the gene as 17 HER2. It's a widely-used expression marker to 18 classify a subtype of breast cancer, and I can 19 tell you about its importance if you'd like. 20 Q. Were you familiar with the HER2 gene 21 at Dana-Farber prior to August of 2009? 22 A. I knew about HER2 for a very long 23 period of time. HER2 positive breast cancer is 24 a subtype of breast cancer that affects about 15 25 percent of individuals with breast cancer. It's	1 as of 2009, I probably could have outlined why 2 that might be useful. 3 Q. Was there a desire in the field in 4 the 2009 time period to engage in single-cell 5 analysis for gene expression as compared to bulk 6 analysis? 7 MS. RAYMOND: Objection. Form. 8 Scope. 9 A. So the question you're asking would 10 depend on the context. I've outlined here at 11 least one example where analysis of HER2 12 expression could have been valuable. How 13 widespread that would have been in the field as 14 of 2009, I'm not prepared to offer an opinion on 15 today. 16 Q. What was the level of interest in 17 performing single-cell analysis as compared to 18 bulk analysis for gene expression in 2009? 19 MS. RAYMOND: Objection. Scope. 20 A. So I haven't done that analysis. I'm 21 not prepared to offer an opinion today. If we 22 talk about breast cancer, I can tell you why 23 HER2 is important. It's a cell surface receptor 24 that promotes cell growth. And as I said 25 earlier, it's clinically relevant.

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1 Q. In terms of just your memory of your 2 time working on the gene expression prior to 3 August of 2009, were you aware of interest in 4 the community in single-cell analysis as 5 compared to bulk analysis? 6 MS. RAYMOND: Objection. Scope. 7 A. It would depend on the type of 8 analysis one wanted to do. As I mentioned 9 earlier, by 2009, I was working with some groups 10 doing analysis of circulating tumor cells. So 11 there was definitely some interest in being able 12 to understand what was happening with individual 13 cells. 14 Q. Did you personally pursue any effort 15 to perform single cell analysis as compared to 16 bulk analysis prior to August 2009, you or your 17 lab? 18 A. So it would depend on how you define 19 single-cell analysis. I don't recall as of 2009 20 all the techniques that we were using. It's not 21 something I prepared or reviewed in preparation 22 for my deposition today or in preparing the 23 declaration I filed. So sitting here today, I 24 don't recall. 25 Q. If you turn to page 15 and 16 of your	1 polynucleotide that's included in the tag 2 polynucleotide be the entire sequence of the 3 sample polynucleotide? 4 MS. RAYMOND: Objection. Scope. 5 A. So a polynucleotide is typically 6 either RNA or DNA in its native state in a 7 molecule and there are different flavors and 8 varieties of DNA that we can discuss. But as a 9 series of nucleotides, hence a polynucleotide, 10 that series of polynucleotides for any 11 individual molecule is referred to as its 12 sequence. 13 So the polynucleotide now has a 14 sequence and that is the sequence of the 15 polynucleotide. 16 In this context, that sequence I 17 believe refers to the entire sequence of the 18 polynucleotide and from a sample polynucleotide 19 of the plurality. So each individual 20 polynucleotide is going to have its own 21 sequence. And the tag polynucleotides also 22 comprise a multiplex identifier sequence. And 23 that multiplex identifier sequence comprises a 24 first tag sequence associated with the cell from 25 which it was derived and a second tag sequence
Page 71	Page 73
1 report. 2 A. All right. 3 Q. And you referred me to the claims as 4 broken up by Dr. Cooper. 5 Do you see that? 6 A. Yes, I do. 7 Q. Okay. 8 In terms of the polynucleotide of 9 Step 1D, do you have that in front of you? 10 A. Yes, I do. 11 Q. Okay. 12 It states there that it comprises a 13 sequence from a sample polynucleotide of the 14 plurality of sample polynucleotides. 15 You see that, right? 16 A. Yes, Step 1D. 17 Q. Right. 18 And in terms of the sequence from the 19 sample polynucleotide that is included in the 20 tag polynucleotide, does that have to be the 21 entire sequence from the sample polynucleotide? 22 MS. RAYMOND: Objection. Scope. 23 A. Would you repeat your question, 24 please? 25 Q. Can the sequence from the sample	1 in Step 1F distinguishing the sample 2 polynucleotide from other sample 3 polynucleotides. So the polynucleotide 4 comprises its sequence so that it includes at 5 least that plus these additional tags. 6 Q. When the tag nucleotides are being 7 generated in Step 1C, can that be done using 8 PCR? 9 MS. RAYMOND: Objection. Scope. 10 A. So I haven't -- in the context of 11 preparing this report, I haven't done a full 12 analysis of the '981 patent and what's disclosed 13 in the specification. I was responding to 14 Dr. Cooper's arguments about obviousness. And 15 so I'm not prepared today to render an opinion 16 about all the different ways that sample 17 polynucleotide -- that tagged polynucleotides 18 can be prepared. 19 Q. Do you know whether PCR can be used 20 to generate tag polynucleotides? 21 MS. RAYMOND: Objection. Scope. 22 A. In an abstract -- in the abstract, 23 one could potentially use PCR to generate tagged 24 polynucleotides. We talked about the 25 introduction of universal primers as one way of

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1 doing that earlier -- or one way of generating 2 tag polynucleotides. And there are a variety of 3 different ways to do that. 4 However, in the context of the patent 5 and what the patent is referring to here, I 6 haven't performed that analysis in the context 7 of preparing this report and am not prepared to 8 render an opinion today. 9 Q. Okay. 10 So you're saying you're not prepared 11 to state an opinion as to whether, in terms of 12 claim 1, generating a plurality of tag 13 polynucleotides, whether that can be 14 accomplished using PCR? 15 MS. RAYMOND: Objection. Scope. 16 Counsel, if you want to bring him to 17 a part of his declaration where he disputes 18 this or addresses this, we can talk about 19 it. 20 But in the context of a PTAB 21 deposition, the PTAB depositions are 22 limited to the scope of his declaration. 23 MR. REINES: No, it's fine if he has 24 no -- I mean, I don't understand what the 25 issue is.	1 you hours of review that you'd have to do now 2 because you haven't formulated any opinion on 3 it, right? 4 A. I don't believe there's an opinion 5 about where the generating step appears in the 6 '981 patent, excuse me, presented in my report. 7 If you can point me to that, I'd be happy to 8 discuss it. But otherwise, it's not something 9 that I've prepared to testify about in the 10 deposition today. 11 Q. If PCR is used to take sample 12 polynucleotides and tag them, would that require 13 the use of the entire sequence from the sample 14 polynucleotide? 15 MS. RAYMOND: Objection. Scope. 16 A. So I'm not prepared to render an 17 opinion about a hypothetical approach to 18 practicing the '918 -- sorry, '981 patent. It's 19 not something I prepared to testify about today. 20 And I have not reviewed that, and so I can't 21 render a valid opinion. 22 Q. And in terms of, in Step 1D, the 23 sequence from the sample polynucleotide, do you 24 know whether that has to be the entire sequence 25 from the original sample polynucleotide of
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1 Q. If you don't have an opinion, just 2 state that. That would be perfect. 3 A. I haven't performed an analysis of 4 the scope of the claims of the '981 patent for 5 the -- within the context of my declaration and 6 deposition today, and so I'm not prepared to 7 render an opinion. 8 Q. Turning to the '981 patent, can you 9 show me where the generating step is performed 10 in the figures? 11 MS. RAYMOND: Objection. Scope. 12 A. I'm sorry. I'm not sure where you're 13 referring to the generating -- oh, Step 1C. 14 Q. Yes. 15 A. So I'm not prepared to offer an 16 opinion as to that today. I didn't do that 17 analysis in the context of preparing my report 18 and responding to Dr. Cooper's argument. I'm 19 more than happy to spend the next few hours 20 reading over the patent and performing that 21 analysis, but it's really outside the scope of 22 what I'm prepared to testify about today. 23 Q. So in order to show where the 24 generating tag polynucleotide step is in the -- 25 is amplified in the '981 patent, that would take	1 Step 1B or whether it can be some portion of 2 that if you're using PCR? 3 MS. RAYMOND: Objection. Scope. 4 A. So you're offering a compound 5 hypothetical. The tagged polynucleotide 6 comprises a sequence, right. So the sequence is 7 part of that tagged polynucleotide. The tagged 8 polynucleotide also comprises the multiplex 9 identifier sequence, which comprises a first tag 10 sequence associated with the cell and a second 11 tag sequence distinguishing the sample 12 polynucleotide from other sample 13 polynucleotides. 14 So the polynucleotide has its own 15 sequence and these multiplex identifiers at a 16 minimum. 17 Q. And my question to you is, is it just 18 focusing on 1D? You don't have to read into the 19 record 1E. In terms of 1D where it says that 20 the tag polynucleotide comprises a sequence from 21 a sample polynucleotide, do you have an opinion 22 one way or the other whether that has to be the 23 entire sequence of the sample polynucleotide 24 from Step 1B? 25 MS. RAYMOND: Objection. Scope.

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1 Q. If you're using PCR? 2 A. The tagged polynucleotide is -- the 3 tagged polynucleotide has its own sequence. So 4 I believe you may be confused about the fact 5 that sequence refers to the actual physical 6 structure of the molecule. It might also refer 7 to sequence determined from that molecule. 8 The answer to your question would 9 depend on the context in which it's used. 10 Beyond reading the literal language here, I'm 11 not prepared to render an opinion as to the 12 scope of what that comprising term means in the 13 context of claim 1 of the '981 patent and the 14 deposition we're conducting today. 15 Q. Answering as directly as you can, is 16 the sequence in the tagged polynucleotide in 17 Step 1D, does that have to be the entire 18 sequence of the sample polynucleotide from 1B? 19 MS. RAYMOND: Objection. Scope. 20 Asked and answered. 21 A. So I'm not sure about the context of 22 your use of the word "sequence." I haven't 23 performed that analysis, and I'm not prepared to 24 offer an opinion today. 25 Q. Do you have an opinion one way or the	1 or are those copies from an amplification 2 process? 3 MS. RAYMOND: Objection. Scope. 4 A. So performing such an analysis wasn't 5 necessary for me to respond to Dr. Cooper's 6 arguments, so I haven't performed that analysis 7 and I'm not prepared to offer an opinion today. 8 Q. In the process of going from the 9 sample polynucleotides of Step 1B to the 10 sequencing of the polynucleotides in Step 1G, 11 can you lose some of the sequence from the 12 original sample polynucleotides in Step 1B? 13 MS. RAYMOND: Objection. Scope. 14 Form. 15 A. So I don't believe I've offered an 16 opinion to that in the declaration we're here to 17 discuss. If you can point me to that, I'd be 18 happy to refresh my memory. Otherwise, I'm not 19 prepared to offer an opinion sitting here today. 20 Q. If you turn to paragraph 23 -- excuse 21 me, page 23, paragraph 40. 22 A. Certainly. 23 Q. And there's a reference to, in 24 Linnarsson, the barcode identified as Br. 25 Do you see that?
Page 79	Page 81
1 other as to whether or not the generating 2 plurality of tagged polynucleotides from the 3 plurality of sample polynucleotides can include 4 targeted PCR? 5 MS. RAYMOND: Objection. Scope. 6 A. So I believe you answered -- asked me 7 the question about PCR earlier in the context of 8 claim element 1C as broken out by Dr. Cooper. I 9 haven't performed that analysis of the '981 10 patent, and I'm not prepared to offer an opinion 11 today. 12 Q. Are the sample polynucleotides of 13 Step 1B genomic DNA or amplified 14 polynucleotides? 15 MS. RAYMOND: Objection to form. 16 A. You're referring, I'm sorry, to Step 17 1D? 18 Q. No, no, I'm sorry. Step 1B, as in 19 "boy." 20 So turning to Step 1B, do you have 21 that in front of you? 22 A. Yes, I do. 23 Q. Is the plurality of sample 24 polynucleotides, are those polynucleotides 25 genomic material directly from the single cells	1 A. Yes, I do. 2 Q. Okay. 3 And is that shown in Panel E and F? 4 A. So I don't have the Linnarsson 5 reference in front of me right now. There is a 6 figure caption that appears earlier in the 7 Linnarsson reference. And Linnarsson and the 8 figure caption for Figure 11, I believe, refers 9 to the series of Xs that appear here as 10 representing that barcode. But the barcode Br, 11 that label doesn't appear in the figure panel 12 itself. It does appear later in Figure 1E as 13 Bc, instead of Br. That may have been a typo 14 when -- or an oversight when Linnarsson prepared 15 the figure caption. 16 Q. Do you know what barcode Br, what 17 that's referring to in Panels E and F as you set 18 this forth in your report? 19 MS. RAYMOND: Counsel, would it be 20 possible to give the witness a copy of the 21 reference? 22 MR. REINES: Sure. 23 (Exhibit 1003 was produced.) 24 Q. Here is Exhibit 1003, which is the 25 Linnarsson reference.

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1 A. Thank you. 2 Q. My question is really focused on what 3 you've written in your report, but if reading 4 Linnarsson somehow helps you with that, go 5 ahead. 6 A. Well, you're asking me explicitly 7 about the barcode and where it's labeled. If we 8 look at Linnarsson on the bottom of page 6, 9 sorry, page 5 of -- well, the Bates number has a 10 6, the page number is 5, it's the last line. 11 And so I may or may not have pulled the entirety 12 of this out into the report, but I definitely 13 refer to the figure caption for Figure 11. And 14 it says, "As a consequence, the 3' end of the 15 cDNA will carry the barcode (XXXX)." 16 So there are four Xs and that's the 17 barcode that's referred to. Later on where I 18 quote here, it talks about the Br, the next 19 page, line 5. So it doesn't explicitly tell us 20 that barcode is the Xs, and it seems to leave Br 21 out of the figure. 22 So those are the places I referred to 23 earlier, the Xs and the Br. 24 Q. Is the barcode in Linnarsson the same 25 thing as the cell tag, what you refer to as cell	1 bottom of page 24 says, referring to Figure 3, 2 the cell tag is shown as now a series of five 3 Xs. 4 Q. Prior to August of 2009, were you 5 aware of cell tags such as in this Illumina 6 publication based on your ownership of an 7 Illumina system? 8 MS. RAYMOND: Objection. Scope. 9 Q. The filing date is March 2009. 10 A. So I hadn't seen this Illumina patent 11 application as of March of 2009 or, I guess, 12 issued patent as of March of 2009. I don't 13 recall what products Illumina might have had on 14 the market at the time. I don't recall if this 15 had been discussed at some of the conferences 16 that I had attended. 17 So for this particular application, I 18 can't say as to whether or not I'm familiar with 19 what Linnarsson was referring to here. 20 Q. Were you generally familiar with cell 21 tags as a nucleic acid technique as of August of 22 2009, you personally? 23 MS. RAYMOND: Objection. Form. 24 A. I'm familiar enough with the concept 25 of multiplex tagging to understand what
Page 83	Page 85
1 tag on page 21 in a couple of spots? 2 A. The cell tag in Figure B where I've 3 called it out and highlighted it is part of the 4 template switching oligo TSO, and this is in 5 paragraph 38 of my report. And I put a box 6 around that cell tag. 7 Linnarsson refers to -- this is a 8 barcode in the figure. I believe elsewhere 9 Linnarsson refers to this as a cell tag. It's 10 used to identify the individual cell that's 11 being labeled and analyzed in this particular 12 step. 13 Q. So when you refer to cell tag with 14 respect to Panel B, that's the same thing as 15 barcode that you referred to in paragraph 40? 16 A. So I've used "cell tag" and 17 highlighted it in a red box, the red box is 18 around the five Xs that appear here. Again, 19 it's interesting Linnarsson uses four Xs in the 20 figure caption, five Xs here. So there's some 21 small inconsistencies. But the cell tag that I 22 referred to here in the red box are the series 23 of Xs and that's what Linnarsson in the figure 24 caption calls the barcode. 25 And, in fact, Linnarsson on the	1 Linnarsson is describing, to understand 2 Dr. Cooper's arguments and to respond to those. 3 Q. Yeah, no, my question is just whether 4 you're familiar with cell tags as of August of 5 2009, very simple question, you personally, 6 Dr. Quackenbush? 7 MS. RAYMOND: Objection to form. 8 A. So it would depend on the use. 9 Linnarsson has a particular use here, and I 10 don't recall when I first heard of Linnarsson's 11 particular application of the term. 12 Q. Let me ask the question again, and 13 try to answer as directly as you can. 14 Were you aware in August 2009 of the 15 use of cell tags in nucleic acid analysis. 16 MS. RAYMOND: Objection. Form. 17 Q. You personally. 18 A. So that's a rather broad question. I 19 mentioned that in the 1990s, when I was at 20 Stanford, Ron Davis and his group were tagging 21 individual yeast cells with what they refer to 22 as zip codes or what are the equivalent of 23 molecular barcodes. They would do experiments 24 in which they knocked out individual genes and 25 inserted those zip codes so that each strain of

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1 yeast had its own; therefore, each cell had its 2 own zip code or barcode. They would grow those 3 yeast strains together in a competitive growth 4 experiment to identify whether particular gene 5 knockouts had a growth effect. And then they 6 analyzed the data by performing a molecular 7 analysis and identifying the barcodes. 8 So in that context, definitely. 9 People had also used a variety of different 10 tags, cell tags in techniques like 11 fluorescence-activated cell sorting to sort 12 individual cell types into individual tubes and 13 then perform molecular analyses on those. 14 So for molecular analysis, there are 15 all sorts of cell tags that people had used. 16 This particular application, I can't tell you 17 when I first came to know about it. 18 Q. Okay. 19 So just to be clear, in terms of the 20 particular cell tag as illustrated in 21 Linnarsson, whether you were aware of that in 22 August of 2009 or not, that's not something that 23 you remember one way or the other; is that fair? 24 A. I don't recall one way or another 25 when I first learned of Linnarsson's specific	1 and I believe the Linnarsson patent appeared in 2 some of those. 3 Q. Do you remember which matter you 4 first saw Linnarsson? 5 A. I don't recall. 6 Q. If you turn to paragraph 44, please. 7 A. All right. 8 Q. Do you have that in front of you? 9 A. Yes, I do. 10 Q. It states here, "Linnarsson's method 11 results in tagging the mRNA molecules extracted 12 from a single cell with the same barcode through 13 the process of reverse transcribing it into 14 cDNA." 15 Do you see that? 16 A. Yes, I do. 17 Q. And the mRNA molecules extracted from 18 a single cell, are you referring there to the 19 actual RNA molecule that was expressed or is 20 this a copy? 21 A. So Linnarsson's method, if I recall 22 it in its entirety, begins with putting 23 individual cells into individual wells in what's 24 referred to as a 96-well microtiter plate. In 25 each well, reagents are added and some of those
Page 87	Page 89
1 application of cell tags. But I understand the 2 concept of multiplex tagging of individual 3 samples well enough to understand what 4 Linnarsson was presenting. I would have 5 understood the patent reading it in 2009. And I 6 understand it well enough to analyze 7 Dr. Cooper's opinions and identify the flaws in 8 Dr. Cooper's arguments. 9 Q. Were you aware of the use of cell 10 tags as described in Linnarsson before this 11 matter, in other words, before you were given 12 the Linnarsson application as part of this 13 proceeding? 14 A. Before 2023, the concept of cell tags 15 was something I was definitely familiar with 16 from a variety of different applications. 17 Q. Including the Illumina applications? 18 A. I've seen the Linnarsson patent 19 before, before 2023, so I was definitely 20 familiar with what Linnarsson presents. 21 Q. What was the context that you saw 22 Linnarsson's publication first? 23 A. I'm not someone who, in the course of 24 my day, typically, reads patents. But as you 25 know, I've served as an expert in other matters,	1 reagents include the template switching oligos, 2 so they're the CDSs, and I would have to look at 3 what CDS is. I always default to something 4 called coding sequence, which is not what it 5 refers to. But it is the sequence which is used 6 to prime first strand -- here it is -- cDNA 7 synthesis primers or CDSs. So a CDS is added. 8 A template switching oligo is added, other 9 reagents are added to each well. 10 The original messenger RNA has a 11 poly-A tail, right, and the original messenger 12 RNA is shown in green, it has a poly-A tail. 13 The CDS in Figure 11 that I've highlighted in 14 red has an oligo (dT) portion and a primer 15 sequence. That primes actually first strand 16 cDNA synthesis. We can talk about some of the 17 details later. 18 So the molecules that are being bound 19 by the CDS are the original molecules that arise 20 -- that appear in the individual cells. 21 I hope I'm answering your question. 22 But what's shown in here in green are 23 the original molecules derived from each 24 individual cell in an individual well in the 25 96-well plate.

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1 Q. When you say derived, do you mean -- 2 A. Those are the molecules that were in 3 that cell. 4 Q. Okay. 5 A. The cells lysed or ruptured to 6 release the mRNAs. 7 Q. Turning to page 28. And this is your 8 discussion of McCloskey? 9 A. Yes. 10 Q. You state, "McCloskey distinguishes 11 alleles of the same gene." 12 Do you see that? 13 A. Yes, I do. 14 MS. RAYMOND: Counsel, if we're 15 turning to Dr. McCloskey, I'd like 16 Dr. Quackenbush to have a copy of that. 17 (Exhibit 1004 was produced.) 18 Q. I'd like to give you Exhibit 1004, 19 which is the McCloskey reference. 20 A. Thank you. 21 Q. Do you see a reference to the random 22 barcode distinguishing alleles in the same gene 23 in McCloskey? 24 A. I see that, yes. 25 Q. And just while you have it, were you	1 art? 2 A. I'm not sure what you mean by 3 "analogous prior art." 4 Dr. Cooper cites to McCloskey, and I 5 respond to Dr. Cooper's arguments. 6 Q. Have you ever given opinions on 7 whether prior art is analogous in your many 8 prior experting efforts? 9 A. I don't -- I don't recall hearing the 10 term "analogous" in the past, so I'm not sure 11 what that means, so I can't -- I can't provide 12 an opinion. I don't recall hearing the term 13 "analogous prior art." 14 Q. While we're on McCloskey, in terms of 15 the what McCloskey was directed to, if you could 16 turn to page 2 of the exhibit. 17 A. Sure. 18 Q. And at the top, McCloskey identifies 19 three issues, contamination, biased 20 amplification and product redundancy. 21 Do you see that? 22 A. The first paragraph, second 23 paragraph? 24 Q. Sorry, the first sentence. Top of 25 the page. Let me ask the question.
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1 familiar with the McCloskey reference when it 2 came out in 2007? 3 A. This is something I can tell you that 4 I definitely didn't see in 2007. It referred -- 5 it's in a pretty obscured journal, and it's 6 discussing a solution to a cross-contamination 7 problem, which is not one of the ones that -- 8 not one of the problems that I was working on 9 directly at the time. 10 Q. I just want to follow up. 11 So you're saying you definitely 12 didn't see this at the time? 13 A. I'm pretty sure I didn't see this in 14 2007. 15 Q. Is that based on the journal? 16 A. It's based on the journal. It's also 17 based on the subject matter. 18 Q. You don't doubt this was published in 19 2007? 20 MS. RAYMOND: Objection. Scope. 21 A. Oh, I have no doubt. I mean, if you 22 look at the date up at the top, it says it was 23 published in 2007. 24 Q. Was it part of your assignment to 25 determine whether McCloskey was analogous prior	1 McCloskey identifies issues of 2 contamination, biased amplification and product 3 redundancy, correct? 4 A. So in that sentence, McCloskey says, 5 talking about DNA sequencing in the prior 6 sentence in the "Introduction," and this 7 sentence states that, "Sequence information 8 obtained by PCR...carries an element of 9 uncertainty..." and it lists the three risks 10 that she asserts; contamination, biased 11 amplification and product redundancy. 12 And then down below immediately 13 describes the potential clinical impact of this 14 being a PRC analysis and sequencing analysis of 15 whooping cough, where cross-contamination was 16 actually the problem that had occurred. 17 So she spends -- she mentions these 18 things, but the one she describes is the problem 19 of cross-contamination. 20 Q. And one of the other issues that the 21 McCloskey paper addresses is redundant sequences 22 from the same cell? 23 MS. RAYMOND: Objection to form. 24 Q. You can turn to page 6 if that helps. 25 You can probably remember.

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1 A. So I'm sorry, where do you see this? 2 Q. The second paragraph, the "Results 3 and Discussion" is focused on it. 4 A. So I don't believe your 5 characterization of that was correct. She says 6 redundant sequences recovered from the same PCR 7 reaction are readily identified because they're 8 identical in both barcode and batch-stamp. 9 Q. And you'll agree that redundant 10 sequences is an issue that the tagging method of 11 McCloskey is also directed in addressing beyond 12 contamination? 13 MS. RAYMOND: Objection. Form. 14 Q. If there's something complicated 15 about that, let me know. 16 A. So McCloskey doesn't specifically say 17 that she's addressing the quote/unquote problem 18 of redundancy. McCloskey in her paper describes 19 an analysis of a single gene, a gene called 20 FMR1, and a bulk tissue sample. And the reason 21 I know it's a bulk tissue sample, she describes 22 the analysis of 2.71 micrograms of DNA. The 23 amount of DNA in a single cell is about 6 24 picograms, so substantially thousands of times 25 less. And what she's referring to here is her	1 redundant sequences. But remember we talked 2 earlier about McCloskey identifying this problem 3 or working on trying to solve this problem of 4 contamination. And in the previous paragraph, 5 she says "Contaminant sequences were identified 6 by batch-stamps assigned to separate reactions, 7 (Fig. 1). The appearance of sequences bearing 8 inappropriate batch-stamps enable us to trace 9 contaminated sequences..." blah, blah, blah. 10 So this is consistent with my 11 previous statement that McCloskey's -- the 12 problem she was really trying to solve was this 13 problem with cross-contamination between PCR. 14 She talks in the introduction about this problem 15 of whooping cough being detected in individuals 16 with -- who didn't have it because of PCR-based 17 contamination. 18 And so that seems to be the problem 19 she's addressed and solved. She also says that 20 by using the randomly-generated barcode, she can 21 distinguish between the different alleles, but 22 she doesn't necessarily talk about removing them 23 or what she's doing. 24 Q. Do you see in that same paragraph 25 that you're looking at now where it says,
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1 ability in that DNA, looking at a single gene, 2 to be able to identify both alleles -- and so 3 alleles are different forms of the same gene. 4 Since we inherit DNA from both our mothers and 5 our fathers, we tend to carry two copies. 6 Sometimes the variants can be distinguished. 7 But the individual copies of those molecules 8 she's able to identify using what we talked 9 about earlier, the randomly-generated barcode to 10 identify allele copies. 11 So she describes she was able to do 12 that. She doesn't describe that as a problem 13 that has been solved. 14 Q. Do you see where it says, "In 15 addition to distinguishing valid from 16 contaminant sequences, our methods detect 17 redundant sequences arising from the same 18 cellular DNA template"? 19 A. Yes, I see that. 20 Q. And are you denying that the tagging 21 of McCloskey is being identified as a way of 22 removing redundant sequences from the datasets? 23 MS. RAYMOND: Objection. Form. 24 A. So McCloskey doesn't describe 25 removing DNA sequences. She describes detecting	1 "Identifying redundant sequences and removing 2 them from data sets is especially important..."? 3 A. I'm sorry, where? 4 Q. The same place, the second full 5 paragraph under "Results and Discussion," the 6 same one. 7 A. Okay. 8 So she says, "Identifying redundant 9 sequences and removing them from the data sets 10 is especially important when analyzing mosaic 11 samples, which occur in both genetic and 12 epigenetic diseases." 13 So a mosaic occurs -- 14 Q. I'm just asking if you saw it. 15 A. I see it, yes. 16 Q. Okay. 17 And in terms of -- are you denying 18 that McCloskey is saying that one of the 19 benefits of the tagging approach is that you can 20 identify redundant sequences and remove them 21 from the analysis? 22 A. So she's talking about specific 23 examples like mosaic samples. The easiest 24 example is going to be a tumor sample where you 25 have a mix of mutated DNA appearing in tumor

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1 cells and normal DNA in infiltrating 2 lymphocytes. And if you wanted to count how 3 many tumor cells, then being able to identify 4 and count the mutant alleles is something she 5 asserts could be done in those mosaic samples. 6 So in doing this bulk analysis, which 7 she does and describes, that kind of molecular 8 counting could be important for applications 9 like tumor analysis. 10 Q. Okay. 11 But just like a simpler question, in 12 addition to addressing contamination, McCloskey 13 also states that her tagging approach can detect 14 redundant sequences such that they can be 15 removed from the analysis, at least under 16 particular -- and gives an example, right? 17 A. In bulk samples, that's something she 18 asserts her method can do. 19 Q. Okay. 20 MR. REINES: By the way, it's -- we 21 can go off the record for a second. 22 VIDEOGRAPHER: We're going off the 23 record at 11:52. 24 (Luncheon recess.) 25 VIDEOGRAPHER: Back on the record at	1 an opinion. 2 Q. Do you know whether the reflex method 3 as described in the '981 patent embodies the 4 claims in the '981 patent? 5 MS. RAYMOND: Objection. Form. 6 Scope. 7 A. So I don't believe Dr. Cooper offers 8 opinions about whether or not the reflex method 9 is embodied in the claims of the '981 patent. 10 The figure legend says that this is, I believe, 11 an exemplary embodiment, but I haven't performed 12 the analysis, and I'm not prepared to offer an 13 opinion. 14 Q. Embodiment of -- it doesn't say an 15 embodiment of the claims, does it? 16 Or is that how you read it? Do you 17 read this where it references that Figure 3 is 18 an embodiment, to be an embodiment of the claims 19 that issued on the '981 patent? 20 MS. RAYMOND: Objection to form. 21 A. I haven't performed the analysis, and 22 I'm not prepared to offer an opinion. 23 Q. Do you know whether the nucleic acid 24 sequence in Step 202 is the same as the nucleic 25 acid sequence in Step 7?
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1 12:38. This begins Media Unit 3 in the 2 deposition of John Quackenbush, Ph.D. 3 BY MR. REINES: 4 Q. If you could open up the '981 patent. 5 A. All right. 6 I have it. 7 Q. First of all, did you review and 8 understand the '981 patent in formulating your 9 opinions in this case? 10 A. Yes, I did. 11 Q. And with respect to Figure 3, in 12 Step 7, the original -- there's sequence from 13 the original sample polynucleotide. 14 That's the Illumina, correct? 15 A. So I don't believe Dr. Cooper offered 16 any opinions about Figure 3. Reading column 2 17 of the patent, it says, "FIG. 3 is a schematic 18 diagram illustrating an exemplary embodiment for 19 moving a primer site and a MID...", a molecular 20 identifier "...to a specific location in a 21 nucleic acid of interest." 22 So I haven't performed an analysis of 23 exactly what's happening in each step of this 24 seven-step figure in the context of the patent. 25 And so at this moment, I'm not prepared to offer	1 A. So I'm not sure what you're referring 2 to by "sequence." Is it the sequence or all of 3 the sequence? I haven't performed that 4 analysis, and I'm not prepared to offer an 5 opinion sitting here right now. 6 Q. Is there any version of the reflex 7 method in the '981 patent that embodies the 8 claimed inventions of the '981 patent? 9 A. So I don't believe Dr. Cooper 10 rendered an opinion about what you're referring 11 to as the reflex method, so I haven't performed 12 that analysis and can't offer an opinion sitting 13 here today. 14 Q. Does the '981 patent have any 15 embodiment of the claimed inventions of the '981 16 patent? 17 A. I'm assuming it does, but I haven't 18 performed that analysis and can't point you to 19 those embodiments. 20 Q. Back to McCloskey, if you would. 21 A. Sure. 22 Q. In the second sentence of the 23 "Results and Discussion," it refers to 24 "...unique cell or allele copy-specific 25 barcodes."

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1 Do you see that? 2 A. Yes, I do. 3 Q. And do you understand that to be two 4 different types of barcodes? 5 MS. RAYMOND: Objection. Form. 6 A. So in the sentence you're referring 7 to in McCloskey, she points to Figure 1. In 8 Figure 1, the only thing that she labels is a 9 randomly-generated barcode identified as the 10 allele copy. And in the caption for Figure 1, 11 she simply refers to a barcode. So I'm assuming 12 that she's using the "or" here to have two 13 specific adjectives to refer to the same barcode 14 that she might refer to as a cell or 15 allele-specific barcode. 16 In the example that she provides in 17 her paper, she actually doesn't have the 18 capability of tracking things back to individual 19 cells. She can only point to specific alleles. 20 Q. Do you understand what's referenced 21 here with the unique cell-specific barcode? 22 A. So she doesn't provide any examples 23 of that in her paper. In the experiment she 24 describes doing here with the sequencing of the 25 FMR1 gene from a bulk DNA sample where cells	1 place before the tagging in McCloskey, if that's 2 what you're saying? 3 A. So McCloskey describes a single 4 experiment. And this experiment is an analysis 5 of the gene called FMR1. And she talks about 6 doing an analysis in which, on page 5 of the 7 document, document page 765, in the section 8 entitled "Sequenase v2.0 (USB) Extension," Human 9 genomic DNA (2.71 micrograms) was cleaved with 10 HinfI from (Boehringer Mannheim GmbH) and 11 another enzyme, AluI, A-l-u-I, and then 12 describes that further analysis of the aliquot, 13 10 percent of that digested genomic DNA. 14 So the fact that she's doing this 15 analysis on 2.71 micrograms of DNA is an 16 indication that she's not using individual 17 cells. Cells contain about 6 picograms of DNA, 18 so about a thousand times less. And so her 19 analysis has got to be on DNA from multiple 20 cells. Therefore, there's no way to know, based 21 on her tagging, which individual cell any 22 molecule came from. 23 Q. Would a person of ordinary skill in 24 the art have known that tagging needs to take 25 place before pooling in order to use barcodes as
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1 from many DNAs were mixed -- excuse me -- in 2 which DNA from many cells is mixed, therefore, 3 I'm not sure specifically what she's referring 4 to here. 5 Q. Do you have any idea at all? 6 A. She refers to Figure 1. And in 7 Figure 1, she only describes allele-specific 8 barcodes. She doesn't provide any examples of 9 cell-specific barcodes. And given the 10 experiment she describes, there's no way to 11 identify and trace any sequence back to an 12 individual cell. And I actually refer to that 13 in paragraph 48 of my declaration on page 30. 14 I write, "Single-Cell analysis 15 requires separate tagging of polynucleotides for 16 each cell prior to pooling to ensure that the 17 same source identifying tag is introduced only 18 to nucleic acids from the same cell." 19 Q. And what are you relying on in 20 McCloskey for the statement that the pooling -- 21 the tagging must take place after the pooling? 22 A. I'm sorry, would you repeat the 23 question? 24 Q. What are you relying on in McCloskey 25 for your statement that the pooling has to take	1 cell-specific barcodes? 2 A. So I'm not sure about the context of 3 your question, but if you had a pool of DNA from 4 a large number of cells, each cell has two 5 copies of the FMR1 gene. And so any individual 6 molecule I look at in that pool of hundreds, if 7 not thousands, of cells, or DNA from that many 8 cells, couldn't be traced back to an individual 9 cell. So the only way to do that, and 10 Dr. Cooper talks about the Linnarsson reference 11 - not the only way - but Linnarsson describes a 12 way of tagging individual cells. Linnarsson 13 describes cell tags, which I believe he refers 14 to as either cell tags or barcodes. And those 15 are introduced in individual cells of 96-well 16 microtiter plate. 17 Q. All right. 18 If you look at the last sentence of 19 McCloskey's results, is that in front of you? 20 A. Yes, it is. 21 Q. And that states, "We recommend that 22 batch-stamps and barcodes be used when 23 amplifying irreplaceable DNAs and cDNAs for 24 forensic, clinical, single cell, and ancient DNA 25 analyses."

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1 Do you see that? 2 A. Yes, I do. 3 Q. And is that consistent with your 4 reading of McCloskey as to what they're 5 recommending? 6 A. So McCloskey actually repeats this 7 sentence twice. First, at the last sentence in 8 the Abstract and then also the last sentence in 9 the Results. 10 So she's making this recommendation 11 and talking about irreplaceable DNAs and cDNAs, 12 and she talks about forensic analysis where, you 13 know, she's clearly, I would guess, addressing 14 the question of cross-contamination, but I don't 15 know. That seems to be the major thrust of her 16 work. Clinical data, single-cell analysis, 17 ancient DNA analysis. It's not exactly clear to 18 me what she's talking about here except these 19 are rare samples in which you would want to 20 avoid cross-contamination. She clearly doesn't 21 describe the use of her method for any kind of 22 single-cell analysis. 23 Q. You'll agree that she recommends the 24 batch-stamps and barcodes that she described for 25 single-cell analysis?	1 And so the batch-stamp is what she's using to 2 identify the contaminants. 3 Q. As you understand the McCloskey 4 reference, what is the purpose of the barcode if 5 you have the batch-stamp to address 6 contamination issues? 7 A. So she says on the second page of her 8 paper, "The random barcode distinguishes among 9 sequences arising from different cell or allele 10 copies." And there's another place where she 11 refers to the barcode as distinguishing between 12 copies of an allele for a particular gene in the 13 sample -- oh, sorry, that's what I described. 14 But sequences arising from different cell or 15 allele copies. 16 So remember earlier we talked about 17 the fact that we have two copies of our genome, 18 so we potentially have two different alleles 19 with variants, and the batch-stamp can be used 20 to identify those. 21 She also talked about mosaic samples, 22 right, tumor and normal cells mixed with each 23 other, where you would expect the tumor to carry 24 certain mutations that the normal cells 25 wouldn't. And so in the kind of bulk sample
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1 MS. RAYMOND: Objection to form. 2 A. So she says she recommends it, but 3 she doesn't describe any way in which this could 4 be done. And the only method that she presents 5 is one that uses 2.71 micrograms of DNA, which 6 is far more than what you would get for an 7 individual cell. 8 All the processing steps involving 9 cleavage and other analyses to analyze the 10 single gene in a single cell, even that would be 11 incredibly difficult. A single gene, excuse me, 12 even that would be very difficult to do in a 13 single cell given the small quantity of DNA and 14 all the losses that would happen with every step 15 that she includes. 16 Q. And in terms of the contamination, 17 that is addressed by the batch-stamp, is that 18 correct, as compared to the barcode? 19 A. So she tells you the batch-stamp is 20 unique to each experiment. And she also tells 21 us in her discussion of the results on page -- 22 document page 6, page -- I don't know what the 23 final page is, but that we talked about earlier 24 that the contaminant sequences were identified 25 by batch-stamps assigned to separate reactions.	1 analysis that could be done, the barcodes can 2 help distinguish between those two types of 3 cells. 4 Q. Why does McCloskey propose doing 5 anything more than just using batch-stamps for 6 what you identify as the contamination issue? 7 MS. RAYMOND: Objection. Form. 8 A. Sorry. Could you repeat the 9 question, please? 10 Q. Okay. 11 Let me try it this way: In 12 McCloskey, does the cell-specific barcodes, do 13 you understand them to be addressing 14 contamination? 15 MS. RAYMOND: Objection. Form. 16 A. So I don't think McCloskey refers to 17 cell-specific barcodes. Well, so the sentence 18 you read earlier talks about unique cell or 19 allele copy-specific barcodes. It refers to 20 Figure 1. In Figure 1, she talks about the 21 randomly-generated barcodes to identify allele 22 copies. 23 You know, what all her motivations 24 are, I can't speak to, but -- 25 Q. Well, let me ask -- go ahead.

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1 A. You know, I just want to say that 2 given the experiment she describes with 2.71 3 micrograms of DNA, you couldn't trace any of the 4 alleles or any of the molecules back to any 5 particular cell. 6 Q. In terms of the barcodes, do you 7 contend that the barcodes in McCloskey are 8 directed to the contamination issue? 9 MS. RAYMOND: Objection. Form. 10 Q. I just want to be clear on that. 11 A. So I haven't thought through all the 12 ways in which one might be able to use the 13 random barcodes to potentially identify 14 contamination. I don't believe that McCloskey 15 discusses that. So she refers to the 16 batch-stamp as being used to identify 17 contamination. And the portion that she refers 18 to as a barcode, the 7-base oligonucleotide to 19 distinguish between alleles in these bulk 20 samples. 21 So I think most of her 22 cross-contamination, at least the way she 23 describes it, points to the batch-stamp as being 24 the primary way; but, again, I haven't thought 25 through all the possibilities.	1 sequences, our methods detect redundant 2 sequences arising from the same cellular DNA 3 template (Fig. 1)." 4 So in that mix of DNA, each template 5 molecules from a cell, and she's saying that her 6 combination of batch-stamps and barcodes can 7 identify places where, in the final sequencing 8 reaction, that same original molecule is counted 9 twice from the same cellular DNA template. 10 Q. And in terms of the clinical use of 11 cDNA, how would that -- how would barcodes help 12 in that context? 13 MS. RAYMOND: Objection. Form. 14 A. So McCloskey doesn't define -- 15 doesn't describe the analysis of cDNA. She 16 describes the analysis of a single gene FMR1 and 17 a sample of genomic DNA coming from what I 18 expect is a bulk tissue sample, although she 19 doesn't really tell us. It could be from a cell 20 culture. I don't know where she gets her DNA. 21 But she doesn't describe applications to cDNA, 22 and she doesn't -- she doesn't talk about this 23 -- the use of these other than a way of 24 measuring template diversity or analyzing mosaic 25 samples.
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1 Q. Will you agree that McCloskey 2 describes the use of tags to address issues 3 other than contamination? 4 A. So I don't know if it's addressing 5 issues. But she does talk about the use of 6 these barcodes, right, as distinct from the 7 batch-stamps to -- well, she says Valid 8 sequences were identified by their date and 9 sample-specific batch-stamp and their unique 10 cell or allele-specific barcodes. 11 So I'm not sure how she's defining 12 validity here, but there may be other issues 13 she's trying to address with the barcodes and 14 the batch-stamps together since she includes 15 them both as being key to identifying valid 16 sequences. 17 Q. Based on your review of McCloskey, 18 what issues do you think she's proposing to 19 address with the barcodes? 20 MS. RAYMOND: Objection. Scope. 21 Form. 22 A. So she says at the beginning of the 23 second paragraph in the "Results and 24 Discussions" section of her paper, "In addition 25 to distinguishing valid from contaminant	1 Q. Would a skilled artisan in 2009, such 2 as yourself, know how to use the McCloskey 3 tagging with cDNA, as she recommends? 4 MS. RAYMOND: Objection to form. 5 A. So McCloskey's ability to identify, 6 right, she says, "An additional benefit of our 7 method...is that counting sequences with 8 nonredundant barcodes provides a quantitative 9 measure of template diversity." 10 So if you want to see how many 11 individual templates are there, then given her 12 method, right, and she describes the use of this 13 with genomic DNA, her analysis, to the best of 14 my read, labels the genomic DNA molecules that 15 she eventually sequences with individual 16 barcodes. And I'd have to go back and review 17 all the details of her method. 18 To be able to cut DNA with an enzyme 19 as she describes, you'd actually have to create 20 double-stranded cDNA. You would be somewhat 21 removed from the individual molecules. 22 So I haven't thought through all the 23 ways in which one could potentially adapt this, 24 but as it's described here, it would be -- it 25 would be -- it would take -- I haven't thought

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1 of different ways in which to describe the use 2 of this method she discloses to analyze cDNA, 3 and I don't believe Dr. Cooper proposes a 4 particular adaptation of McCloskey's method as 5 described here in detail for the analysis of 6 cDNA. 7 Q. Would you in 2009 have been able to 8 apply the barcodes of McCloskey to cDNA? 9 MS. RAYMOND: Objection to form. 10 Scope. 11 A. So I haven't thought through the way 12 in which one might do that. As I mentioned, as 13 laid out here, this method would be difficult as 14 written, as described in this paper, to describe 15 -- to directly to apply to cDNA. 16 I could attach barcodes to lots of 17 different molecules. Whether it would achieve 18 the goal she lays out here, I'd have to think in 19 more detail about how one would actually go 20 about doing that. 21 Q. Do you have any explanation for why 22 McCloskey and her team recommended using her 23 barcodes for single-cell analysis? 24 MS. RAYMOND: Objection to form. 25 Scope.	1 Dr. Cooper pointed to any. There certainly was 2 literature about multiplex analysis of cDNA 3 samples, but I don't know if there's any 4 analysis of single-cell cDNA samples. I would 5 assume that Dr. Cooper would have pointed those 6 out if he had been able to find them. I did no 7 search for them. 8 Q. If you turn to page 4 of the exhibit, 9 under the heading of "Barcode." 10 A. All right. 11 Q. And here, McCloskey states, "The 12 number of distinguishable barcodes in a 13 population of oligonucleotides used in a 14 reaction is determined by the number of random 15 bases, n. This enables one to distinguish among 16 4n allele copies per reaction." 17 Do you see that? 18 A. Yes, I do. 19 Q. And do you understand "n" there to be 20 a variable? 21 A. So the way it's presented in the two 22 sentences you read and is a variable, she then 23 states, "We currently use seven nucleotides for 24 the barcode, giving 16,384 possible barcodes for 25 each encoding oligonucleotide."
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1 A. So single-cell analysis can mean a 2 variety of different things. And one of the 3 reads that one could place here in that sentence 4 that we referred to earlier, the last sentence 5 in the paper, also the last sentence in the 6 abstract, which is the only place she mentions 7 or uses the phrase "single cell," she doesn't 8 make it clear what she's proposing here; how one 9 would go about doing that, given the method 10 that's outlined. She could be talking simply 11 about the analysis of a single cell as opposed 12 to other methods, like Linnarsson, which 13 Linnarsson describes, I believe, as single-cell 14 analysis. Or I believe the '918 [sic] patent 15 also uses the phrase "single-cell analysis," 16 although I don't recall all of the details. 17 So this could simply be a reference 18 to analyzing single cell. But, again, the 19 method she describes here would be difficult to 20 implement for a single cell. 21 Q. Was there literature on the use of 22 barcoding in the context of cDNA for single 23 cells as of 2009? 24 MS. RAYMOND: Objection. Scope. 25 A. So I don't know if -- I don't believe	1 And I believe Dr. Cooper in his 2 analysis suggests the use of McCloskey's 3 barcodes which she describes as seven 4 nucleotides. 5 Q. And did you understand from McCloskey 6 that the number of possible barcodes could be 7 increased or decreased by changing the number of 8 random bases used in the barcode? 9 MS. RAYMOND: Objection. Scope. 10 Q. Is that what it's teaching? 11 A. So McCloskey doesn't describe that. 12 A read of this is that one could choose the 13 number of random bases n. But the number of 14 bases one chooses is going to depend on a 15 variety of different experimental constraints 16 and goals. 17 And in the context of what we're 18 discussing today, Dr. Cooper's analyses, I don't 19 believe Dr. Cooper provides any suggestion that 20 the number of bases be chosen to be anything 21 other than n when he suggests adapting 22 McCloskey's batch-stamp and barcode to the 23 analysis of single cells as laid out in 24 Linnarsson. 25 Q. When McCloskey says "We currently use

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1 seven nucleotides for the barcode...," do you 2 understand McCloskey to be saying that that 3 wouldn't be changeable if the experiment 4 warranted it? 5 MS. RAYMOND: Objection. Form. 6 Scope. 7 A. So there are a variety of different 8 considerations that would go into this. 9 McCloskey's barcodes have a very particular -- 10 or the oligonucleotides that contain the 11 barcodes have a very particular structure. So 12 they have a target-specific region that would 13 bind to a particular genomic target locus or 14 genomic target sequence, potentially a gene 15 sequence or some other element. They have the 16 batch-stamp. And I don't recall immediately how 17 long that batch-stamp is. There's her seven 18 randomly-generated barcode. There's some 19 additional sequences to give her little hairpin 20 structure. It's a three-dimensional structure 21 and then some additional bases that bind to, I 22 believe, the genomic region. 23 So she's got a very particular 24 structure that she's using in her analysis. And 25 I don't know the entirety. I haven't really	1 MS. RAYMOND: Objection. Form. 2 Scope. 3 A. So there are a wide variety of 4 considerations one would have to look at in 5 adjusting that length, and a lot of it would 6 have to do with the experimental conditions. So 7 one of the things I point out in my report is 8 that Dr. Cooper states, and I agree, that one 9 would need many more copies of a molecular tag 10 that - and I'm quoting Dr. Cooper here - I 11 really am quoting the patent in column 22, lines 12 54 to 57. "In general, to accomplish such 13 molecular tagging the number of distinct MID 14 tags to be used should be many times greater 15 than the actual number of molecules analyzed." 16 All right. So that's one 17 consideration one would have to look at. 18 And then Dr. Cooper, in his report on 19 page -- paragraph 256, tells us that tagging 20 each molecule would require at least a hundred 21 times more tags than sample polynucleotides. 22 So if I look at the 7 mers that 23 McCloskey uses, she has 16,000 possible 24 barcodes. That tells me that, according to 25 Dr. Cooper's logic, she should be able to tag
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1 done an analysis for what the impact would be in 2 expanding this barcode or in what conditions one 3 might be able to do it and for what particular 4 application. 5 So, yeah, there are a lot of things 6 you could potentially vary, but she doesn't 7 provide any guidance on how to do that or why 8 one would want to do it. 9 Q. A person skilled in the art reading 10 McCloskey would understand that you would want 11 to increase the number of random bases in the 12 barcode if you were addressing a situation where 13 you would have more different molecules than you 14 would barcodes, right? 15 MS. RAYMOND: Objection. Form. 16 Scope. 17 A. So would you repeat the question, 18 please? 19 Q. A person skilled in the art reading 20 McCloskey would understand that you would want 21 to increase the number of random bases in the 22 barcode if you were addressing a situation where 23 you would have more different molecules than you 24 would have barcodes if you were using the seven 25 nucleotide barcode?	1 about 160 different molecules. 2 One might envision you can make that 3 longer, but, again, it would depend on your 4 application. 5 So on page 6 of McCloskey, she talks 6 about sequence recovery and talks about 7 performing DNA sequencing which was carried out 8 using fluorescent dideoxynucleotides in applied 9 -- using BigDye terminator chemistry from 10 Applied Biosystems, and one skilled in the art 11 would understand that this is an implementation 12 of Sanger sequencing. 13 At the time, in 2009, the reads were 14 over a thousand bases long, so adjusting that 15 size of a barcode might be -- might not have an 16 impact on what you're actually able to do with 17 the rest of the sequence. 18 I believe at the time, the sequencing 19 technologies, the Illumina sequencer read 35 20 bases, maybe 50, in 2009. And so adjusting that 21 number could have a significant impact on other 22 aspects of the experiment. 23 So, you know, you'd really have to 24 think through how to do it. It's not just 25 simply, Oh, I'm going to make this longer

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1 without having any potential impact on the rest 2 of it. And Dr. Cooper doesn't propose a way to 3 make this longer without negatively affecting 4 other aspects of the incorporation of these kind 5 of barcodes in Linnarsson. 6 Q. If you turn to page 32, please. 7 A. Of my report? 8 Q. Your report. 9 A. Sure. 10 All right. I'm there. 11 Q. You state in the middle of paragraph 12 51, "In certain embodiments, the MID on a 13 polynucleotide is used to identify the source 14 from which polynucleotide is derived." 15 Do you see that? 16 A. Yes, I see that. 17 Q. And what did you mean by that, 18 derived? 19 A. So you're referring me to a section 20 in my report in which I discuss claim 21 construction and how to interpret different 22 terms. 23 In paragraph 51, I say, I have 24 assumed the following constructions in my 25 analysis, both of which are found in the	1 individual cell and then to trace it back to a 2 specific polynucleotide, a specific molecule 3 that came from that same single cell. 4 Q. So when you say trace it back to a 5 polynucleotide, is that referring to the 6 original biological material or a copy? 7 MS. RAYMOND: Objection. Scope. 8 Form. 9 A. So I'm not sure how you're defining 10 "copy," and I'm not sure the context in which 11 you're looking at defining a copy. 12 Now we're talking about the language 13 of the patent. And the MID, as we see in 14 column 6, can be used to identify the source 15 from which the polynucleotide is derived. The 16 multiplex sequence comprises a first cell tag 17 associated with the single cell from which the 18 sample polynucleotide is derived and a second 19 tag sequence distinguishing the polynucleotide 20 from other sample polynucleotides derived from 21 the same cell. 22 I don't believe Dr. Cooper contests 23 this, and so I haven't done a fulsome analysis 24 to really look at the breadth and scope of what 25 that might be referring to. And I'm not
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1 specification of the '981 Patent: Multiplex 2 Identifier or (MID), it means a tag or 3 combination of tags associated with a 4 polynucleotide whose identity - right - the tag 5 DNA sequence can be used to differentiate 6 polynucleotides in the sample, which is what you 7 referred me to. 8 If I look at that, and I'm 9 interpreting the claims of the patent, the MID, 10 this multiplex identifier, comprises a first tag 11 sequence associated with a single cell from 12 which a sample polynucleotide is derived, and a 13 second tag sequence distinguishing the sample 14 polynucleotide from other sample polynucleotides 15 derived from the same cell. 16 So if I'm reading this in the context 17 of the line you quoted, which comes from 18 column 6, lines 33 to 38, and it goes further, 19 "In certain embodiments, the MID on 20 polynucleotide is used to identify the source 21 from which that polynucleotide is derived," if I 22 read that in the context of the '981 patent, 23 that MID is going to have a component, an 24 element which allows me to trace each 25 polynucleotide, each molecule back to an	1 prepared to offer an opinion beyond what is 2 presented in my report. I don't believe 3 Dr. Cooper contests that. 4 Q. In paragraph 51, you say, and this is 5 in your Claim Construction section, "...sample 6 means 'a quantity of material from a biological, 7 environmental, medical, or patient source in 8 which detection, measurement, or labeling of 9 target nucleic acids is sought.'" 10 Do you see that? 11 A. I see that, yes. 12 Q. And there, you're -- that's what you 13 understand is the construction of the term 14 "sample" as used in the claims; is that correct? 15 Let me ask the question again. 16 A. All right. 17 Q. In paragraph 51, you state, "I have 18 assumed the following constructions in my 19 analysis." 20 Do you see that? 21 A. Yes, I do. 22 Q. And then you have the terms from the 23 claims that you're construing are in quotes: 24 multiplex identifier, MID, and sample; is that 25 right?

Page 126 1 A. So I'm not offering an extensive 2 claim construction analysis here. I'm providing 3 definitions which I don't believe Dr. Cooper 4 contests. These definitions are derived from 5 the patent itself. "Sample," I quoted part of 6 the first sentence of the very long paragraph 7 that describes samples. And the claim itself 8 tells us the sample comprises a plurality of 9 single cells and then goes on to discuss that 10 further. 11 So, you know, the sample I'm taking 12 here to mean in the context of the report I 13 filed today or that we're discussing today in 14 which Dr. Cooper, in response to Dr. Cooper, a 15 sample is a quantity of material from a 16 biological, environmental, medical, patient 17 source or patient source in which detection 18 measurement or labeling of target nucleic acids 19 is sought. 20 Q. You stated you provided two 21 constructions from the specifications of the 22 '981 patent in paragraph 51. 23 What are the two? Can you just 24 identify the terms construed? 25 A. So I'm not offering a claim	Page 128 1 material that's at the source rather than a copy 2 of it; is that right? 3 A. I'm not sure how one would copy a 4 chunk of tissue. 5 Q. You understand the term "sample" is 6 used also to describe the polynucleotides in 7 claim 1, correct? 8 MS. RAYMOND: Objection. Form. 9 A. So I don't believe I provided an 10 analysis of that in my report. It wasn't 11 necessary to respond to Dr. Cooper. I'd have to 12 think about that analysis in greater detail, and 13 I'm not prepared to offer an opinion today. 14 Q. Do you know what sample 15 polynucleotide means in the claims in the '981 16 patent? 17 A. In the context of responding to 18 Dr. Cooper's arguments, I believe that my use of 19 the term "sample polynucleotide" is consistent 20 with the way in which he uses it. And so I'm 21 not responding or I'm not offering claim 22 construction opinions with regard to the '981 23 patent. I'm providing definitions only to the 24 extent that I'm able to respond to Dr. Cooper's 25 arguments.
Page 127 1 construction for the entirety of the '981 2 patent. That would be outside the scope of what 3 I'm providing. 4 I'm responding to Dr. Cooper's 5 analyses. And I believe that the two terms, 6 "molecular identifier MID" and "sample" as 7 described in paragraph 51, quoting two portions 8 in the '981 patent, are consistent with 9 Dr. Cooper's analysis. 10 Q. Okay. 11 And did you, in fact, assume the 12 construction of sample to be a quantity of 13 material from a biological, environmental, 14 medical or patient source in which detection, 15 measurement or labeling of target nucleic acids 16 is sought? 17 A. That's the assumption of the 18 definition of that term I made in the context of 19 responding to Dr. Cooper and his arguments. And 20 I believe that's consistent with Dr. Cooper's 21 arguments regarding obviousness of the '981 22 patent claims and in his analysis of Linnarsson, 23 McCloskey. 24 Q. In terms of the term "sample," you 25 understand sample to mean the actual biological	Page 129 1 Q. Did you disagree with the way 2 Dr. Cooper applied any of the claim terms for 3 the '981 patent? 4 MS. RAYMOND: Objection. Form. 5 A. So that's a rather broad question. 6 I don't have Dr. Cooper's report available in 7 front of me to look through it. 8 Dr. Cooper, I think, misapplies a lot 9 of terms. Dr. Cooper offers a lot of vague 10 suggestions without really describing in detail 11 what he means in many places. 12 I have many pages in which I talk 13 about some of the shortcomings in Dr. Cooper's 14 analyses. I'd be willing to walk through those 15 if you want to talk about specific examples. 16 Q. With respect to plain and ordinary 17 meaning, you applied -- excuse me. 18 With respect to sample 19 polynucleotide, you applied the plain and 20 ordinary meaning, correct? Paragraph 52. 21 A. In responding to Dr. Cooper's 22 arguments, wherever possible, I applied the 23 plain and ordinary meaning as they would have 24 been understood in light of the specification. 25 I don't believe I offer any particular

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1 construction or interpretation of sample 2 polynucleotide beyond the plain and ordinary 3 meaning. 4 I always, to the best of my ability, 5 try to respond to the opinions as presented by 6 Dr. Cooper. 7 Q. Do you understand that the '981 8 claims are limited to mammalian sources? 9 MS. RAYMOND: Objection. Scope. 10 A. I haven't performed such an analysis. 11 I don't believe Dr. Cooper offers any such 12 opinions, and so it's beyond the scope of what 13 I'm prepared to testify about today. 14 Q. In terms of Linnarsson, is it your 15 understanding that Linnarsson can only be used 16 with mammalian sources? 17 MS. RAYMOND: Objection. Scope. 18 A. So I don't believe Dr. Cooper offers 19 any interpretation of Linnarsson saying that 20 Linnarsson can only be used for mammalian 21 sources. I don't believe I offered any opinions 22 about the limitations of the application of 23 Linnarsson beyond mammalian sources. However, 24 Linnarsson's CDS, cDNA synthesis primer has an 25 oligo(dT) component. And to the best of my	1 BY MR. REINES: 2 Q. Can you identify any reason why the 3 Linnarsson approach wouldn't be applicable in 4 the eyes of a skilled artisan to yeast cells? 5 MS. RAYMOND: Objection. Scope. 6 Form. 7 A. So I don't believe Dr. Cooper makes 8 any arguments about the limitations of the 9 application of Linnarsson. And so I'm not 10 prepared to offer an opinion as to what the 11 limitations might be sitting here today. 12 MR. REINES: Okay. Why don't we take 13 a break. Thanks. 14 VIDEOGRAPHER: Off the record at 15 1:40. This ends Media Unit No. 3. 16 (Recess.) 17 VIDEOGRAPHER: On the record at 1:53. 18 This begins Media Unit 4 in the deposition 19 of John Quackenbush, Ph.D. 20 BY MR. REINES: 21 Q. Based on your analysis of 22 Dr. Cooper's declaration, have you identified 23 any terms that warrant claim construction? 24 MS. RAYMOND: Objection. Form. 25 Scope.
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1 recollection, all eukaryotic mRNAs are 2 polyadenylated. 3 So, for example, Linnarsson's 4 application or Linnarsson's method could, 5 sitting here today speculating, could be applied 6 to analysis of single yeast cells or other 7 eukaryotic cells. 8 Q. Would you have known in 2009 how to 9 adapt the Linnarsson method to single yeast 10 cells? 11 MS. RAYMOND: Objection. Scope. 12 A. So I haven't fully done that 13 analysis, but if yeast cells, if -- and I 14 believe they are; I believe the mRNA is 15 polyadenylated. I could imagine using it for 16 yeast cells. But, again, I haven't fully 17 thought through all the implications, and so I 18 haven't thought about what one would want to do 19 in 2009, other than analyzing the methods 20 presented here in Linnarsson in the context of 21 Dr. Cooper's arguments. 22 MS. RAYMOND: If we could take a 23 break in the next couple of minutes, that 24 would be great. 25 MR. REINES: Sure.	1 THE WITNESS: Do you want to repeat 2 that for him? 3 MS. RAYMOND: Objection. Form. 4 Scope. 5 A. So I didn't perform a thorough 6 analysis with regard to claim construction. My 7 opinions are laid out in the section of my 8 report we referred to earlier, which I believe 9 appears on claim 31. Beyond that, I don't have 10 any further opinions to offer. 11 Q. Did you say claim 31? 12 A. Page 31. 13 Q. Oh, okay. 14 But I'm saying if you had seen any 15 area where, you know, based on Dr. Cooper's 16 report, where there was a need for claim 17 construction, you would have identified that; is 18 that right? 19 MS. RAYMOND: Objection. Form. 20 Scope. 21 A. I didn't perform that analysis, other 22 than what's offered in Section C on page 31 and 23 32 of my report. I was simply trying to respond 24 to Dr. Cooper's arguments as best I could. 25 Q. Did you perform any analysis to see

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1 if there was any claim construction that was 2 warranted in view of Dr. Cooper's report? 3 A. I didn't perform an analysis to see 4 whether or not claim construction was warranted. 5 I responded to Dr. Cooper's arguments in the 6 context of the claim construction I presented 7 here. 8 Q. One of the terms you offered for 9 claim construction was the term "sample." 10 Does the definition that you identify 11 in paragraph 51 apply to the term "sample" as 12 used in the phrase "sample polynucleotide" in 13 the claims? 14 MS. RAYMOND: Objection. Form. 15 A. I haven't fully analyzed the term 16 "sample polynucleotide." If you can point me to 17 places in Dr. Cooper's report where he offers a 18 construction, I'd be happy to review it and 19 comment on it. 20 Q. No. My question was different. 21 You give a definition for the term 22 "sample" that you used in your analysis. 23 Did you use that definition of 24 "sample" as it relates to the phrase "sample 25 polynucleotide" in the claims?	1 of the '981 patent have a very particular 2 structure, particularly in the claims. 3 And the terms "barcode" are often 4 used loosely in a variety of different ways in 5 the '981 patent. 6 Dr. Cooper specifically talks about 7 different types of barcodes, so the barcode that 8 appears in Linnarsson, the batch-stamp plus 9 barcode that appears in McCloskey, another type 10 of barcode that appears in Hug. And so this is 11 just to be very clear about what the MIDs were 12 in claim 1 since that was at the heart of 13 Dr. Cooper's arguments. 14 I don't recall exactly why I included 15 "sample" here. I'd have to look back at 16 Dr. Cooper's report. 17 Q. If you turn to Linnarsson and 18 specifically Figure 3. 19 A. All right. 20 Q. And with respect to the molecule 21 shown in Figure 3, that includes a cell tag; is 22 that right? 23 A. That's what the figure says, yes. 24 Q. And what is the purpose of the cell 25 tag in the molecule of Figure 3?
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1 MS. RAYMOND: Objection to form. 2 A. So I didn't perform an analysis of 3 the term "sample polynucleotide" as laid out in 4 the claims of the '981 patent because I don't 5 think -- I didn't believe it was necessary to 6 respond to Dr. Cooper's arguments. 7 Q. You only included the constructions 8 of the terms in your report where you thought it 9 was necessary in view of Dr. Cooper's report; is 10 that correct? 11 A. My exercise in carrying out this work 12 was to respond to Dr. Cooper's analysis 13 presented in his report. I don't have his 14 report sitting in front of me right now, and I 15 don't recall if he offered any independent or 16 contradictory constructions. But the 17 constructions I used are laid out in paragraphs 18 51 through 52 of my report. 19 Q. And how did you select which terms to 20 include construction of in paragraph 51? 21 A. Again, I don't have Dr. Cooper's 22 report sitting in front of me. I don't recall 23 why these were selected. 24 Particularly, MID I believe it was 25 important because the MID laid out in the claims	1 A. So Figure 3 is only showing the 2 construction of -- if you look at the 3 description of the drawing that occurs on page 5 4 of Linnarsson, it's an example of a template 5 switching oligonucleotide that has a five prime 6 amplification primer sequence or (APS), a cell 7 tag and a three prime sequence for template 8 switching. 9 So, I mean, here, it's just labeling 10 the components of the TSO. So in the figure 11 itself, it's not ascribing any particular use to 12 the cell tag, but I believe the cell tag is 13 described in greater detail in Figure 11. 14 But, in general, the cell tag is used 15 to distinguish each of the 96 wells -- a unique 16 cell tag is assigned to each of the 96 wells in 17 Linnarsson's 96 well plate and is used to 18 identify the cell which is placed into that 19 plate and the molecules derived from it. 20 Q. And if you turn to Figure 4 -- 21 A. All right. 22 Q. -- do you have opinions regarding 23 Figure 4 in this matter? 24 MS. RAYMOND: Objection. Form. 25 A. So -- go ahead.

Page 138 1 Q. I didn't see any reference to 2 Figure 4 in your report, and I just want to 3 know, do you have a reason for that? 4 A. So I didn't call Figure 4 explicitly. 5 The caption for Figure 4 says it "...shows an 6 example of cDNA synthesis primer, (CDS) 7 comprising a 5' amplification primer sequence 8 (APS), a cell tag and a 3' RNA complementary 9 sequence (RCS)." And that's showing the 10 different segments here. 11 This is, I believe, something that 12 Linnarsson refers to as an alternate form of his 13 CDS. It's not the form of the CDS that appears 14 in either Figure 11 which provides an outline of 15 the method that Linnarsson is describing in his 16 patent. And this method in Figure 11 is also 17 consistent with the two examples, Example 1 and 18 2 that appear in the patent. 19 Dr. Cooper notes, and I believe this 20 is stated in Linnarsson, that a cell tag could 21 be used in either the TSO or the CDS. So to the 22 extent that Dr. Cooper makes arguments about the 23 cell tag appearing in the CDS, I discussed that 24 in my response without necessarily explicitly 25 calling out Figure 4.	Page 140 1 A. You would have to ask Dr. Linnarsson 2 why he didn't include it there and why he 3 included the cell tag in Figure 4. He doesn't 4 offer an explanation and I can't speculate. 5 Q. Do you know why there's no cut site 6 in Figure 4? 7 A. Again, you would have to ask 8 Dr. Linnarsson why he chose not to do that. 9 Q. Do you have any understanding why 10 there's no identification of biotin in Figures 3 11 and 4? 12 A. Again, I can't comment on why 13 Dr. Linnarsson made certain choices in preparing 14 his figures. I have no way of knowing. 15 Q. Using the Illumina Genome Analyzer 16 that you had at Dana-Farber, were you able to 17 create cDNA libraries without fragmentation? 18 MS. RAYMOND: Objection. Scope. 19 A. I don't recall all the details of the 20 cDNA library sequencing that I did at 21 Dana-Farber. I don't believe it's germane to 22 the arguments that Dr. Cooper presents in his 23 report and that I responded to. 24 Q. Right, but my question wasn't any of 25 that. It was just when you -- or maybe you
Page 139 1 Q. Do you know what the sequence is of 2 the cut site used by Linnarsson? 3 A. So by "the cut site," I believe 4 you're referring to BST CL1. [sic] Off the top 5 of my head, I don't know the recognition 6 sequence for that restriction enzyme. 7 Q. Did you look it up? 8 A. At some point, I probably did, but I 9 don't recall what it is. 10 Q. And why did you want to know what the 11 sequence is of the cut site? 12 A. There are different types of 13 restriction enzymes and I believe I looked just 14 to make sure it was a Type 1 restriction enzyme. 15 Q. And how did you look it up? 16 A. NEB is the biggest supplier of 17 restriction enzymes, New England Biolabs. I 18 think I probably looked it up on their website; 19 I don't recall. The sequence of the BST CL1 20 [sic] recognition site wasn't important for the 21 analysis I performed, and I don't believe 22 Dr. Cooper made any particular arguments about 23 it. 24 Q. And in terms of Figure 3, how come 25 there's no cut site in Figure 3?	Page 141 1 don't remember, but when you used cDNA libraries 2 with the Illumina Genome Analyzer, did you use 3 fragmentation? 4 MS. RAYMOND: Objection. Scope. 5 A. So I don't recall all of the details. 6 We may or may not have fragmented molecules. It 7 would depend on the particular application we 8 were interested in. 9 Q. And which applications would you tend 10 to have wanted to fragmented cDNA libraries? 11 MS. RAYMOND: Objection to form. 12 Scope. 13 A. Again, there are a lot of reasons why 14 one might or might not do particular things in a 15 particular laboratory setting. Thinking back to 16 what I was doing 15 years ago, yeah, I haven't 17 thought back and done that analysis and I'm not 18 prepared to do it right now. 19 Q. Yes, it wasn't an analysis. It's a 20 memory. 21 Let me ask it this way: When you 22 were creating cDNA libraries, would you be more 23 inclined to use fragmentation if the sequences 24 were longer? 25 MS. RAYMOND: Objection to form.

Page 142 1 A. In creating cDNA libraries, you get 2 typically cDNA -- you get all-comers, so long 3 and small cDNAs. Again, it would depend on the 4 particular application and what one wanted to 5 do. 6 There are a whole host of different 7 experiments. You could do surveys of all the 8 RNAs. You can do analyses of a subset. You can 9 do mutational analysis. It would depend on the 10 particular goal of the experiment. 11 Q. For the experiment example that 12 Linnarsson includes, do you have an 13 understanding why he would use fragmentation for 14 that cDNA library, based on your review of 15 Linnarsson? 16 A. So there are a variety of different 17 reasons why Linnarsson may have fragmented the 18 molecules. Probably the simplest to understand 19 is that Linnarsson eventually uses the biotin to 20 bind the ends of the molecule to streptavidin 21 beads, and then uses BTS CL1 to release the five 22 prime fragment ends from the beads and then does 23 further processing in preparation of doing 24 sequencing. 25 So part of it is to release the five	Page 144 1 this is reflected in Linnarsson's description of 2 Figure 11. So Panel C is a step that involves 3 PCR using single primers. And in that reaction, 4 the single primers are biotinylated. The 5 fragments are then cut, in Figure D, with I 6 believe two enzymes. I believe that's what he 7 -- or, actually, I don't recall. I think maybe 8 one enzyme. I'm thinking of McCloskey where 9 there are two enzymes. And I'd have to look and 10 see -- oh, I'm sorry, not with restriction of 11 enzyme, but with DNAs. So it's a general enzyme 12 that digests DNA. And he refers to this as a 13 fragmentation step that randomly cleaves the 14 double-stranded DNA. And he then describes 15 binding the two ends to streptavidin beads. 16 Streptavidin beads are typically magnetic beads 17 coated with streptavidin. 18 So you can bind both ends of these 19 fragments and then wash away the fragments that 20 aren't bound. So the internal fragments that 21 were cut with DNAs now are washed away. 22 And what Linnarsson then describes in 23 Panels E and F is the binding of these fragments 24 in Step E using BTS CL1 to cut the BTS site and 25 release the barcode, and then doing some
Page 143 1 prime end as part of the overall strategy to 2 release the five prime ends. There are other 3 reasons why one might choose to do that. Again, 4 it would depend on a particular downstream goals 5 and applications. 6 Q. In the example in Linnarsson where he 7 uses biotin, do you have an understanding as to 8 why he uses biotin? 9 MS. RAYMOND: Objection. Scope. 10 Q. Let me ask the question again. 11 Based on your understanding of the 12 Figure 11 example in Linnarsson, why -- what is 13 your understanding is the purpose of using 14 biotin and then the cutting site and attaching 15 it to the bead and doing the wash and then 16 cutting it? 17 MS. RAYMOND: Objection. Form. 18 A. So I think you got the order wrong 19 and I lay out it doesn't bind and cut, it cuts 20 and then binds. And I lay this out starting 21 with the detailed description of Figure 11 that 22 begins on page 19. 23 On page 22, I talk about Panels C and 24 D, and I've sort of grouped them together. 25 So Panel C -- and, again, some of	Page 145 1 additional steps to put on P1 and P2, which, if 2 I recall correctly, are the sequencing primers 3 that are used. 4 So there are a variety of different 5 reasons why one would do this. One of them is 6 simply to be able to release the five prime 7 ends, which if both the five prime and three 8 prime ends were bound, if one were to cut with 9 BTS CL1, the molecule of the cDNAs, the 10 double-stranded cDNAs would still be attached to 11 the streptavidin beads, so you couldn't carry 12 out the Steps E and F. 13 Q. My question is maybe simpler, which 14 is why use biotin at all and perform a wash? 15 A. There are a variety of different 16 reasons, including the fact that he was very 17 interested in purifying these segments of the 18 five prime end, those segments containing the 19 cell tag. These internal segments wouldn't 20 contain the cell tag. They would interfere with 21 -- they would participate in the end repair and 22 ligation of the primers for sequencing. And 23 they -- I mean, there could be a variety of 24 other reasons why Linnarsson chose to do it, but 25 the simplest reason for including biotin is

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1 because he was interested in doing a 2 purification to isolate the fragments that 3 included the cell tag. 4 Q. Let me ask you this question: If you 5 were creating a cDNA library without 6 fragmentation, would there be any reason in 7 Linnarsson to use biotin and the wash? 8 MS. RAYMOND: Objection. Form. 9 Scope. 10 A. Linnarsson describes the use of 11 biotin, and so I'm not going to speculate on 12 other things that Linnarsson could have done. 13 This is what Linnarsson did. And so in the 14 context of Dr. Cooper's arguments that 15 Linnarsson plus McCloskey is invalidating prior 16 art, I relied on what Linnarsson described as 17 his overall approach. 18 Q. Let me ask it this way: In 19 Linnarsson, is there any purpose for the biotin 20 and the BTS sequence other than to support the 21 fragmentation approach? 22 MS. RAYMOND: Objection. Form. 23 Scope. 24 A. Biotin with streptavidin beads is 25 commonly used as a way of purifying molecules.	1 that's why Linnarsson uses biotin and BTS 2 sequence in his experiment is for purification 3 or do you have an opinion one way or the other 4 on that? 5 A. So Linnarsson doesn't describe in 6 detail why he does it. I haven't performed a 7 detailed analysis of all the reasons why. But 8 if we read beyond Figure D, if we go to Figures 9 E and F, if one didn't purify the samples and 10 then in going from E to F did end repair and 11 ligation of different molecules, different 12 primers, all of those molecules would be 13 labeled. All of the molecules would be 14 sequenced. 15 There are many more molecules 16 potentially that represent these internal 17 fragments and the other fragments. Those 18 internal fragments, the way Linnarsson describes 19 his approach, would not contain the cell tags. 20 They don't have cell tags. 21 And so there's -- you know, 22 Linnarsson is what Linnarsson is. And I'm not 23 in a -- I wasn't required to speculate about 24 other things Linnarsson could have done or why 25 Linnarsson did different things, because
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1 Biotin and the use of BTS CL1 is used to cleave 2 and then further analyze the five prime 3 fragments. So it's what Linnarsson describes as 4 doing. 5 I haven't done an analysis to think 6 about other approaches that Linnarsson could 7 have used, and Dr. Cooper doesn't provide any 8 speculation about that that I was in a position 9 to respond. 10 Q. Do you have any -- have you performed 11 any analysis as to what the purpose might be for 12 biotin in the BTS site and the streptavidin 13 beads in Linnarsson beyond supporting 14 fragmentation? Have you done an analysis of 15 that? 16 MS. RAYMOND: Objection to form. 17 Scope. 18 A. So I don't believe Dr. Cooper offers 19 any theories as to the use of biotin and BTS CL1 20 that would differentiate it from what Linnarsson 21 actually describes and proposes. 22 As I mentioned, the use of biotin and 23 streptavidin beads is a common approach for 24 purifying the DNA samples. 25 Q. Do you have an opinion as to whether	1 Dr. Cooper didn't offer any suggestions as to 2 alternative implementations of Linnarsson. 3 Q. If you turn to page 46 of Linnarsson. 4 A. All right. 5 Q. In the method of claim 1, the cDNA is 6 synthesized from mRNA -- well, let me start 7 again. 8 Do you have claim 1 in front of you? 9 A. Yes, I do. 10 Q. In Linnarsson, the cDNA library is 11 generated according to the method of claim 1 12 without any fragmentation or use of biotin, 13 correct? 14 MS. RAYMOND: Objection. Form. 15 A. So I don't believe Dr. Cooper 16 provides an analysis of claim 1 in his report. 17 I haven't included an analysis -- consequently, 18 I have not included an analysis of each step of 19 claim 1 or each step of the claimed invention in 20 my report. And so I haven't performed a 21 sufficient analysis to be able to tell you 22 exactly what is encompassed in the scope of 23 claim 1 as presented in Linnarsson. 24 Q. So did you review claim 1 when you 25 reviewed Linnarsson?

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1 A. I reviewed it, but I didn't review it 2 in great enough detail to answer your question, 3 because Dr. Cooper didn't provide any opinions 4 that I was required -- that required a response. 5 Q. Okay. 6 But you can see in claim 1, there's 7 no reference to fragmentation, correct; there's 8 no fragmenting step? 9 A. I haven't read all of claim 1, and I 10 haven't read it in the context of the written 11 description to fully understand what Linnarsson 12 is claiming. And I don't believe Dr. Cooper 13 offered any analysis and so I'm not prepared to 14 offer an opinion today as to what it 15 encompasses. 16 Q. Okay. 17 So you're saying you can't answer the 18 question whether there's a fragmentation step in 19 claim 1 of Linnarsson? 20 A. I haven't analyzed claim 1 to the 21 extent where I would feel confident offering an 22 informed opinion sitting here today. 23 Q. All right. 24 And you understand that the claims of 25 the Linnarsson patent are part of the disclosure	1 And his assertion that Linnarsson, as he 2 describes it, represents invalidating prior art. 3 Q. If you could turn to Figure 11, if 4 you could, please. 5 A. Sure. 6 All right. 7 Q. In terms of Figure 11, did you -- 8 it's the other page? 9 A. It's right here (indicating). I'm 10 looking at the caption. 11 Q. Okay. 12 For Figure 11, did you believe that 13 the CDS is released for sequencing according to 14 this method? 15 A. So the CDS is the three prime 16 fragment end. The way it's depicted in this 17 figure and in both Example 1 and Example 2, 18 which corresponds to this figure, there is no 19 potential release of the CDS as a 20 double-stranded molecule to then be processed 21 through Steps E and F. 22 Q. And why would there be a cell tag if 23 it was never going to be sequenced? 24 A. So Dr. Cooper doesn't provide any 25 arguments as to how one would modify what's
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1 of the patent application? 2 A. I believe that's correct, yes. 3 Q. And then in terms of -- can you see 4 that there's no attachment using biotin in 5 Claim 1? 6 A. Again, I haven't done that analysis 7 and I believe if Dr. Cooper felt it was 8 important to single out claim 1, he would have 9 done that in his declaration. And I didn't see 10 anything in his declaration making that 11 argument, and so I'm not in a position to render 12 an opinion because I have nothing to respond to. 13 Q. And with respect to claim 10, do you 14 see where it says that both the CDS and the TSO 15 include a tag? 16 A. Yes, I do. 17 Q. Okay. 18 So why would the CDS be tagged if it 19 was never -- if it was attached to a 20 streptavidin and it never cut for sequencing? 21 A. So I haven't done that analysis. 22 Dr. Cooper makes statements about either the CDS 23 or TSO including a tag, but Dr. Cooper doesn't 24 provide an analysis as to how the TSO tag would 25 be read given his description of Linnarsson.	1 presented in Linnarsson to sequence that. I can 2 speculate about ways in which it might be done. 3 But to the extent that Dr. Cooper doesn't 4 provide such an argument, I don't have anything 5 to respond to. 6 Q. For your opinion that -- do you 7 believe Linnarsson requires fragmentation to 8 create cDNA libraries, according to his method? 9 A. So if you use the term "cDNA 10 library," this is a term that Dr. Linnarsson 11 actually defines in his patent on page 12, 12 starting at line 4. The term "cDNA library" 13 refers to a collection of cloned complementary 14 DNA, cDNA fragments, which together constitute 15 some portion of the transcriptome of a single 16 cell or a plurality of single cells. 17 So Dr. Linnarsson's description of 18 the cDNA library, and the library is what is 19 eventually sequenced, consists of cDNA 20 fragments. So it at least suggests that the 21 cDNA library has undergone this fragmentation 22 step. 23 Q. But do you have an opinion one way or 24 the other? 25 A. As to?

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1 Q. Do you have an opinion one way or the 2 other as to whether Linnarsson requires 3 fragmentation for the creation of cDNA libraries 4 using his tagging methods? 5 A. So I haven't done that analysis. If 6 I look at Figure 11 and Examples 1 and 2, which 7 are the examples presented, Linnarsson's method 8 uses this fragmentation step using DNAs and this 9 is consistent with his definition of the term 10 "cDNA libraries" which appears on page 12. 11 Q. If you go to claim 27, please. 12 A. Of? 13 Q. I'm sorry. Of Linnarsson. 14 A. All right. 15 I'm there. 16 Q. And you see that there's a claim step 17 added. It says, "Wherein the processing 18 comprises fragmenting the cDNA library"? 19 A. I see that in claim 27. 20 Q. Okay. 21 And you understand that's a dependent 22 claim? 23 A. Yes, that's my understanding. 24 Q. And you understand that the normal 25 claim construction rules are that a dependent	1 theories for obviousness. 2 Q. And you understand that part of 3 Dr. Cooper's opinion was based on Figure 4 of 4 Linnarsson? 5 A. I don't have Dr. Cooper's -- 6 (Exhibit 1002 was produced.) 7 Q. I'd like to show you Exhibit 1002. 8 A. Thank you. 9 All right. 10 Q. You understand that Dr. Cooper for 11 his opinion relied on the Linnarsson disclosure 12 at least in part based on Figure 4? 13 A. So where does Dr. Cooper refer to 14 Figure 4? 15 Q. Here is one example, page 79 at 16 paragraph 165. 17 Do you see the reference to Figure 4? 18 A. Yes, I do. 19 Q. And then I think in 166 and so forth. 20 Did you evaluate Linnarsson as a 21 whole as to whether the Linnarsson method claim 22 1 without fragmentation was something that was 23 taught by this reference, including Figure 4? 24 MS. RAYMOND: Objection. Form. 25 MR. REINES: Well, that seems like a
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1 claim is presumed to add something that is not 2 otherwise required by the independent method 3 claim? 4 MS. RAYMOND: Objection. Form. 5 Scope. 6 A. So my general understanding of 7 dependent claims is that they add some 8 additional requirements, but I haven't done a 9 full analysis of the claims, the independent and 10 dependent claims appearing in Linnarsson. 11 Q. When you reviewed claim 1 of 12 Linnarsson to understand that this patent 13 disclosure for purposes of your obviousness 14 analysis, did you recognize that there was no 15 fragmenting step in claim 1 in terms of the 16 generating the cDNA library? 17 MS. RAYMOND: Objection. Form. 18 A. So I don't believe Dr. Cooper 19 presented a claim-by-claim analysis of the 20 Linnarsson patent. My report was responding to 21 the theories presented by Dr. Cooper. And so to 22 the extent that Dr. Cooper didn't perform such 23 an analysis, I didn't feel it was incumbent upon 24 me to perform such an analysis. I can only 25 respond to what Dr. Cooper offered as his	1 valid objection. Let me ask the question 2 again. 3 Q. Did you evaluate whether Linnarsson, 4 Figure 4 -- let me start again. 5 How come you never addressed 6 Figure 4? 7 MS. RAYMOND: Objection. Form. 8 A. So I don't explicitly call out 9 Figure 4 in my analysis, but I do talk about 10 some of Dr. Cooper's suggestions that 11 Linnarsson's method as presented in Figure 11 in 12 the examples could be modified. 13 One of the suggestions that -- 14 Q. I just asked about your reference to 15 Figure 4. 16 It doesn't refer to Figure 4 there, 17 does it? 18 A. It refers to the CDS, and the CDS is 19 represented in Figure 4. 20 Q. Okay. 21 A. And I can describe in detail why 22 Cooper's suggestions about modifying the CDS 23 fall flat. 24 Q. Understood. 25 Now, with respect to claim 1 and

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1 whether -- did you ever evaluate whether the 2 claim 1 method, which doesn't include a 3 fragmentation step, whether that covers the 4 embodiment of Figure 4? 5 A. So that would be Dr. Cooper's burden. 6 Dr. Cooper doesn't provide a claim-by-claim 7 analysis of Linnarsson. Dr. Cooper makes 8 arguments largely about what's presented in 9 Figure 11. And so in responding to Dr. Cooper, 10 I responded to his assertions about Figure 11 11 and how Figure 11 might be modified. 12 If I look at Figure 4, Figure 4 13 presents the CDS without a BTS sequence and how 14 that would be released in sequence, how it would 15 be joined to -- Dr. Cooper makes some 16 suggestions that you could put a batch or some 17 kind of McCloskey's barcode on the TSO and 18 something else on the CDS and the TSO, but 19 doesn't really explain how those pieces would be 20 put together. 21 So, you know, Dr. Cooper doesn't 22 perform that analysis and so I didn't do it 23 because I didn't have to respond to this 24 analysis. 25 Q. You understood that Dr. Cooper stated	1 facilitate the downstream analysis. 2 Q. So when you reviewed Dr. Cooper's 3 report, you didn't understand that he was 4 stating that there was an alternative disclosure 5 in Figure 4 that was different from what was in 6 Figure 11; is that correct? 7 MS. RAYMOND: Objection to form. 8 Q. Can you answer "yes" or "no" whether 9 you understood that? 10 A. He's not presenting it as an 11 alternative to Figure 11. He's presenting the 12 CDS modification as an alternative to the TSO 13 modification, but what he shows doesn't actually 14 correspond -- 15 Q. Yeah, I'm not asking -- 16 A. I'm sorry -- 17 Q. If you want to argue it -- 18 A. -- I'm not -- 19 Q. -- instead of answering my question. 20 A. I'm answering your question, all 21 right? 22 You're -- I think you're 23 misrepresenting what Dr. Cooper is presenting. 24 Q. All right. 25 Well, it's here and everyone can read
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1 that Figure 4 approach of Linnarsson was an 2 alternative to the approach of Figure 11? 3 A. Could you point me to that, please? 4 Q. Yes. Page 79. Hopefully, it's still 5 open -- 6 A. Yes. 7 Q. -- to that. 8 A. I'm sorry, where on page 79? 9 Q. I'm going to ask the question again. 10 A. All right. 11 Q. Maybe you can follow me. 12 When Dr. Cooper -- when you reviewed 13 Dr. Cooper's report in preparing your own, you 14 understood that he was stating that Figure 4 was 15 an alternative approach to Figure 11, correct? 16 This is at paragraph 165 where he says 17 "alternatively"? 18 A. So I don't believe he's proposing it 19 as an alternative to Figure 11. I believe he's 20 proposing it as an alternative to putting the 21 cell tag on the TSO. But Dr. Cooper doesn't 22 suggest that -- or doesn't provide a mechanism 23 by which the cell tag -- by which the CDS 24 presented in Figure 4 would actually be 25 substituted into Figure 11 in a way that would	1 it. 2 A. Yes. 3 Q. Okay. 4 A. And he's presenting a modification to 5 the CDS is a modification to the alternative of 6 the TSO. All Figure 3 or Figure 4 shows is a 7 sequence that has an oligo (dT), a cell tag and 8 the universal primer sequence. It doesn't 9 include all the steps in Figure 11. So if 10 you're telling me this is an alternative to 11 Figure 11, that doesn't make any sense. 12 Q. And in terms of why you never 13 referenced Figure 4 in your report, it's because 14 of that, because you didn't view it as an 15 alternative disclosure to Figure 11; is that 16 right? 17 MS. RAYMOND: Objection to form. 18 Foundation. 19 A. So I think you're mischaracterizing 20 all of my prior testimony and what's represented 21 in my report. 22 Q. Okay. 23 We have your report so we're able to 24 see it. 25 A. Yes. And I discussed Dr. Cooper's

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1 theory that one could modify the CDS to include
2 a cell tag and present why that is inconsistent
3 with what's disclosed in Figure 11.

4 Q. In Figure 4, a CDS has a cell tag,
5 correct?

6 A. It has a cell tag, but it doesn't
7 include --

8 Q. I'm just asking you -- you need to
9 just answer my question at some point.

10 In Figure 4, the CDS has a cell tag?
11 It's a simple question. Let's test how
12 responsive you can be.

13 Will you agree with that?

14 MS. RAYMOND: Counsel, please. Treat
15 my witness with respect.

16 A. I agree that it includes a cell tag,
17 but it lacks other key features that would be
18 required to substitute it into Figure 11. And
19 I'd be happy to describe those in detail for
20 you.

21 Q. Okay.

22 And you understood that Figure 4 was
23 just a substitution that you would make to
24 Figure 11?

25 MS. RAYMOND: Objection. Form.

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1 fruit without a bowl to hold it together.

2 Q. And that's the best you can answer
3 that question, correct?

4 A. It wasn't my burden to describe how
5 Dr. Cooper should have presented any kind of
6 argument. Dr. Cooper fails to present a cogent
7 argument that I can respond to.

8 Q. Would you agree that Figure 4 is a
9 tag polynucleotide?

10 A. It's a polynucleotide that contains a
11 cell tag, but it fails -- it's a representation
12 of a polynucleotide that carries a cell tag, but
13 Dr. Cooper fails to disclose how this would work
14 in the workflow of Figure 11.

15 Q. How does -- what does claim 26 --
16 excuse me, claim 27, which states -- for
17 Linnarsson claim 27 where it adds fragmenting
18 the cDNA library.

19 Do you see that?

20 A. Yes, I do.

21 Q. What does that add to the claim 1?

22 A. Dr. Cooper didn't present an analysis
23 of the claims of Linnarsson in the context of
24 representing invalidating prior art, and so I
25 haven't done that analysis because I didn't have

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1 A. Dr. Cooper asserts that without any
2 explanation. Dr. Cooper fails to address the
3 deficiencies that appear in Figure 4, including
4 the lack of a biotin and the lack of the BTS
5 sequence that would be required if one were to
6 even imagine trying to do this. And Dr. Cooper
7 provides no analysis of -- or no description of
8 how this would be substituted in or how it would
9 work in the overall workflow to render the
10 claims of the '981 patent obvious.

11 Q. And do you have an explanation for
12 why there's no biotin or fragmentation in the
13 disclosure of Figure 4?

14 A. Figure 4 is not describing a
15 workflow. Figure 4 is describing an
16 oligonucleotide. So this is Dr. Cooper's burden
17 and Dr. Cooper failed to provide any description
18 of how this would function.

19 Dr. Cooper suggests putting part of
20 the tag or taking McCloskey's tag and splitting
21 it between the TSO and the CDS, but doesn't
22 describe how that would work, how it would all
23 be put together.

24 So Dr. Cooper throws out a lot of
25 little pieces, but he's basically got a bowl of

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1 to do it to respond to Dr. Cooper.

2 Q. And did you -- when you reviewed
3 Linnarsson, did you have any reaction at all to
4 the fact that he described his method for
5 generating a cDNA library not to include
6 fragmenting or the use of biotin?

7 A. I didn't do that kind of detailed
8 analysis because it wasn't required to respond
9 to Dr. Cooper's arguments about obviousness.

10 Q. And you consider that a detailed
11 analysis; is that correct?

12 A. I performed an analysis to the extent
13 that I understood the patent well enough to
14 respond to Dr. Cooper's arguments.

15 If Dr. Cooper had presented arguments
16 about claim 27 - and I don't believe he does -
17 then I would have responded to them in kind.

18 Q. Did you attempt to respond as best
19 you could to Dr. Cooper's point that the
20 Linnarsson disclosure describes a broader
21 approach that doesn't require fragmentation?

22 MS. RAYMOND: Objection. Form.

23 A. So if you can point me to where that
24 occurs in Dr. Cooper's declaration, I'd be happy
25 to comment on it.

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1 If we look at Figure 11, if the 2 molecules in Figure 11 are not fragmented, then 3 if I go from Step D to Step E, if I cut with BTS 4 CL1, all it's going to do is release one end of 5 the molecule not the other, and so the 6 double-stranded cDNA molecule would still be 7 bound to the streptavidin beads and the rest of 8 the workflow wouldn't be possible. 9 Q. But you understand that Figure 11 of 10 Linnarsson is just one embodiment of the 11 inventions -- of that application? 12 A. Dr. Cooper doesn't provide an 13 explanation for how this would work without 14 fragmentation, and so I have nothing else to 15 respond to but Dr. Cooper's arguments. 16 Q. Right. 17 I'm just asking, did you understand 18 that Figure 11 is just one embodiment of the 19 inventions of the Linnarsson patent document? 20 A. Dr. Cooper doesn't discuss any other 21 embodiments and so I had nothing else to respond 22 to. 23 Q. But you do understand that it's one 24 embodiment? 25 A. I haven't done an analysis of all of	1 responded to those. 2 To the extent that Dr. Cooper 3 presented arguments about other potential 4 embodiments, I responded to those. I didn't 5 respond to things Dr. Cooper didn't present. 6 Q. I understand that. 7 Did Dr. Cooper rely on other 8 embodiments other than Figure 11? 9 A. So I'm not sure exactly what you're 10 referring to. Dr. Cooper suggested combining 11 Linnarsson with McCloskey, so I don't know if 12 you would consider that another embodiment. 13 Dr. Cooper suggested including a cell 14 tag in the CDS rather than the TSO or in both 15 the CDS and TSO. To the extent that he proposed 16 that, I responded to it. 17 Q. Do you know whether Dr. Cooper relied 18 on Figure 4 for his opinions in this case? 19 A. Dr. Cooper presents Figure 4. And to 20 the extent that he presents it, you may consider 21 that, meaning that Dr. Cooper relied on 22 Figure 4, but Dr. Cooper doesn't address the 23 deficiencies that appear in Figure 4. 24 Q. And in terms of any explanation you 25 have for not directly addressing Figure 4, why
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1 the patent to the extent that I've looked at all 2 the possible embodiments. Linnarsson may or may 3 not describe it that way. 4 Q. In reviewing Linnarsson for 5 formulating your opinions, did you consider any 6 embodiment of Linnarsson other than Figure 11 7 embodiment? 8 A. I considered what Dr. Cooper 9 presented. Dr. Cooper suggests adding, for 10 example, a cell tag to the CDS, and so I 11 considered that. That doesn't appear directly 12 in Figure 11. 13 Dr. Cooper doesn't describe how that 14 would work, and so I responded to Dr. Cooper's 15 argument to the best of my ability, given what 16 Dr. Cooper presented. I can't respond -- I was 17 not in a position to respond to what Dr. Cooper 18 might have said or might not have said -- or 19 might have said. I can only respond to what he 20 did say. 21 Q. Did you consider any embodiment of 22 Linnarsson other than the Figure 11 embodiment 23 in performing your analysis? 24 A. Again, Dr. Cooper suggested some 25 modifications to what's in Figure 11 and I	1 don't you provide those now if you have them? 2 Why didn't you cite Figure 4 in your 3 report? 4 MS. RAYMOND: Objection. Foundation. 5 A. So, again, I believe you're 6 mischaracterizing what's presented in my report. 7 I'm happy to read through the entire report to 8 find all the places where I discuss the 9 limitations that appear in Figure 4. I didn't 10 directly call them out, but responded to 11 Dr. Cooper's arguments and felt that there was 12 no reason to call out Figure 4 explicitly. But 13 I will point you to paragraph 59 in my report, 14 beginning on page 37. 15 Q. You are mischaracterizing -- 16 A. Repeatedly, Dr. Cooper's theory of 17 modifying Linnarsson's CDS using McCloskey's 18 teaching of a barcode fails for the same reason. 19 All right. So the CDS with now some kind of 20 oligonucleotide. 21 "Although the 3' fragment (the end of 22 the cDNA with the CDS) is not part of the 23 internal portions that are washed away, it is 24 nevertheless not sequenced. As discussed above, 25 only the TSO has a BTS sequence. The CDS does

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1 not." And the CDS is what you're referring to 2 in Figure 4. 3 "The 3' fragment (the CDS end) 4 remains bound to the beads in Panel E." Right? 5 And I cite to the patent, the "'(3' fragments 6 remain stuck on the beads.)'" 7 "Each of the 3' fragments bound to 8 the beads in Panel E is not released for 9 sequencing in Panel F. And nowhere does 10 Linnarsson describe any releasing any 3' 11 fragment from the bead or sequencing it. Thus, 12 Dr. Cooper's theory relying on the 13 Linnarsson-McCloskey combination fails because 14 any tagging in the CDS would be on the 3' 15 fragment, and it would not be sequenced. [as 16 read] 17 All right. So you are absolutely 18 correct, I didn't cite to Figure 4, but I'm 19 explicitly describing Dr. Cooper's modifications 20 or proposed modifications of the CDS appearing 21 in Figure 11 to include some type of tag and 22 that's what Dr. Cooper points to in Figure 4. 23 MS. RAYMOND: I think we've been 24 going for a chunk more than an hour now. 25 If we can take a break.	1 little (i), do you have that in front of you? 2 A. Yes, I do. 3 Q. Okay. 4 It says, "a sequence from a sample 5 polynucleotide of the plurality of sample 6 polynucleotides..." 7 Do you see that? 8 A. Yes, I do. 9 Q. Does that require, in terms of your 10 understanding of the claim, that the entire 11 sequence of the sample polynucleotide is 12 included in the tagged polynucleotide? 13 MS. RAYMOND: Objection. Form. 14 Scope. 15 A. So I haven't done that analysis. I 16 don't believe Dr. Cooper offered any opinions 17 regarding that that I was required to respond 18 to, and so I'm not prepared to offer an opinion 19 about that sitting here today. 20 Q. And in terms of Step (c), it says, 21 "sequencing the plurality of tagged 22 polynucleotides..." 23 Does that tagged polynucleotide have 24 to be -- does that permit additional processing 25 of the tagged polynucleotide from Step (b)
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1 Q. You mischaracterized my question. My 2 question was just why you didn't cite Figure 4. 3 So I move to strike all your argument. 4 MR. REINES: If you want to take a 5 break now, that's fine. 6 VIDEOGRAPHER: Off the record at 7 3:04. This ends Media Unit No. 4. 8 (Recess.) 9 VIDEOGRAPHER: On the record at 3:18. 10 This begins Media Unit 5 in the deposition 11 of John Quackenbush, Ph.D. 12 BY MR. REINES: 13 Q. If you turn to Figure 11 of 14 Linnarsson. 15 A. All right. I'm there. 16 Q. The polynucleotide at the bottom at 17 F, do you see that? 18 A. I see the representation of it, yes. 19 Q. That's tagged, correct? 20 MS. RAYMOND: Objection to form. 21 A. So it has a type of tag. It has 22 Linnarsson's barcode, which I think he refers to 23 as a cell tag. 24 Q. Now, turning to the claims of the 25 '981 patent, claim 1. If you look at (b),	1 before Step (c)? 2 MS. RAYMOND: Objection. Form. 3 A. Again, I don't think Dr. Cooper 4 offered any opinion about additional processing 5 and so I had nothing to respond to. So I 6 haven't done that analysis, and I'm not prepared 7 to offer an opinion today. 8 Q. Do you have an opinion as to whether 9 the sequencing of plurality of tagged 10 polynucleotides requires sequencing of the 11 entire sequence of the tagged polynucleotide? 12 MS. RAYMOND: Objection to form. 13 Q. Is that a claim construction issue 14 that you evaluated? 15 MS. RAYMOND: Objection. Form. 16 Scope. 17 A. So I don't believe Dr. Cooper has 18 offered any opinions, so I haven't done that 19 analysis, and I'm not prepared to offer 20 testimony regarding it today. 21 Q. Okay. 22 Would a user of the Linnarsson 23 process benefit from the advantages promoted by 24 McCloskey of the barcodes that are disclosed in 25 McCloskey of identifying redundant sequences?

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1 MS. RAYMOND: Objection to the form. 2 A. So I'm not sure what you're asking 3 me. I'm not sure that Dr. Cooper presented an 4 analysis of advantages and so I haven't 5 performed that analysis. I'm not prepared to 6 offer an opinion today. 7 Q. I want to ask you -- well, now one of 8 your opinions is that "The biotin on the 5' end 9 in the CDS would block ligation of tag(s) to the 10 CDS." You state this in paragraph 89? 11 A. Yes, correct. 12 Q. And would a person of ordinary skill 13 in the art in 2009 know that you couldn't ligate 14 a barcode to the biotin on the five prime end of 15 the CDS? 16 MS. RAYMOND: Objection. Form. 17 Scope. 18 A. So a person of ordinary skill in the 19 art would understand that if we look at -- the 20 easiest way to understand it is to look at 21 element D of Figure 11, or maybe it's B. Both 22 the five prime and three prime ends of the 23 fragment being analyzed have biotin molecules 24 attached. That biotin is typically attached to 25 the five prime phosphate. And ligation requires	1 how that might have been done. 2 Q. Do you have an opinion whether or not 3 a person skilled in the art would be able to do 4 that? 5 MS. RAYMOND: Objection. Scope. 6 Q. And by "that," I mean ligate a tag to 7 the CDS before placing biotin on the five prime 8 end? 9 MS. RAYMOND: Objection. Scope and 10 form. 11 A. So biotin isn't placed on the five 12 prime end. Biotin is incorporated into the five 13 prime end in the PCR step between Step B and 14 Step C in Figure 11. 15 Dr. Cooper doesn't offer any 16 alternative which would allow such ligation. 17 And so while I can speculate about different 18 ways in which it could possibly be carried out, 19 I wouldn't know all the ramifications unless I 20 thought about that more deeply, and so I'm not 21 prepared to speculate today. 22 Q. Do you have an opinion one way or the 23 other as to whether a person of ordinary skill 24 in the art in 2009 would be able to ligate a tag 25 to the CDS before putting biotin on? Just that
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1 the formation of a phosphodiester bond, as I 2 describe in paragraph 89. So if there's already 3 a biotin attached, you wouldn't be able to 4 create that bond, hence, ligation wouldn't 5 occur. And a person in 2009 would have 6 understood this. 7 Q. Would a person of skill in the art 8 with the knowledge of the techniques described 9 in your report in paragraph 25 know how to 10 ligate a tag to the CDS before placing biotin on 11 the five prime end? 12 MS. RAYMOND: Objection. Scope. 13 A. So I don't think Dr. Cooper presents 14 any analysis of such an approach. Dr. Cooper -- 15 ligation is a reaction that occurs with 16 double-stranded DNA molecules. And sitting here 17 today, I can't conceive of some way in which 18 that would happen. 19 The biotin appears early in the 20 process in this -- on the CDS side, in the 21 construction of the CDS; and on the TSO side, in 22 the PCR step; and in both ends, in the PCR step. 23 Dr. Cooper doesn't provide any 24 suggestion for how that would be handled, and, 25 therefore, I'm not in a position to speculate on	1 question; not how it would be done, but whether 2 it would be within the skill in the art? 3 MS. RAYMOND: Objection. Scope and 4 form. 5 A. So I don't understand what you mean 6 by "before putting biotin on." The biotin is on 7 the primer itself, and so in going from Step B 8 to Step D when those double-stranded molecules 9 are made, the biotin is incorporated. 10 Q. We'll address that case as well. But 11 right now I'm just asking you, would a person of 12 skill in the art know how to adjust the process 13 of Linnarsson, such that the tag could be 14 ligated to the CDS before biotin is introduced 15 to the molecule at the five prime end? 16 MS. RAYMOND: Objection. Form. 17 Scope. 18 Q. Just whether it's within the scope of 19 the skilled level in the art, whether you have 20 an opinion on that. 21 A. So it's a complex question that 22 doesn't have a "yes" or "no" answer. Dr. Cooper 23 doesn't provide an explanation for how that 24 would be done. 25 While one could speculate about

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1 different ways that it could be done, 2 potentially be done, one would have to think 3 about whether or not it would actually be 4 compatible with the rest of what's disclosed in 5 Linnarsson or actually prevent Linnarsson from 6 carrying out the method that's proposed here. 7 So I haven't done that analysis 8 because Dr. Cooper hasn't presented a scenario 9 in which it would have. 10 Q. Is that as responsive as you can be? 11 MS. RAYMOND: Objection. Form. 12 A. If you ask the question again, I'll 13 try to respond more clearly. 14 Q. Okay. 15 Leaving aside how it would be done, 16 do you have an opinion, sitting here now, as to 17 whether it would be within the scope of the 18 competency of a skilled artisan in 2009 to 19 modify the Linnarsson process so that the tag is 20 ligated before biotin is added? 21 MS. RAYMOND: Objection. Form and 22 scope. 23 A. You're asking a question which 24 doesn't have a simple answer and I wish I could 25 give you a simple answer, right. You're saying	1 it's within the level of skill in the art to 2 modify the Linnarsson process to remove the 3 biotin, ligate the tag to the CDS and then put 4 the biotin back on the five prime end? 5 MS. RAYMOND: Objection. Scope. 6 A. So this is outside the scope of what 7 I was asked to do here today. Dr. Cooper 8 presented an obviousness argument based on the 9 combination of Linnarsson and McCloskey. And in 10 my report, I've done a detailed analysis of 11 Dr. Cooper's suggestions. 12 Now you're asking me to invent a 13 completely new process different from 14 Linnarsson, and I haven't sat down to do the 15 analysis of how one might reinvent Linnarsson 16 because that's outside the scope of 17 understanding whether or not Linnarsson, as 18 presented, is invalidating prior art. 19 Q. Would a person of skill in the art 20 have the competency to do it? Do you have an 21 opinion on that? 22 MS. RAYMOND: Objection. Scope. 23 A. It would depend on a lot of factors, 24 and I'm happy to reiterate those as I did 25 previously.
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1 biotin is added. It's not physically added to a 2 double-stranded molecule. It's a part of the 3 synthesis of the double-stranded molecule the 4 way Linnarsson describes it. So that's the 5 first place where I'm having a trouble giving a 6 simple "yes" or "no" answer. 7 Second, while you can imagine ways of 8 removing -- potentially removing the biotin 9 through chemical reactions, I haven't thought 10 through whether or not that would destroy will 11 the rest of the molecule in some way that you 12 couldn't analyze it. 13 So, you know, it would really depend 14 on the application and what you wanted to do. 15 And I don't have a simple answer sitting here 16 today. 17 Q. Do you have any reasonable answer? 18 MS. RAYMOND: Objection to form. 19 A. I think I gave you a very reasonable 20 answer. You presented an incomplete 21 hypothetical and it's impossible for me to 22 respond to. 23 Q. Do you have an opinion whether it's 24 within the scope of the -- let me start again. 25 Do you have an opinion as to whether	1 I haven't done an analysis to 2 understand whether or not it would actually 3 completely disrupt the process in Linnarsson 4 such that it would not carry out its stated 5 goals. 6 Q. Can you be any more direct than that? 7 MS. RAYMOND: Objection to form. 8 A. I think I've been as direct as 9 possible. You could do lots of different 10 things, right. You could ask me, you know, is 11 there a way to modify the wheels on my car and I 12 could describe a way of modifying the wheels 13 such that my car wouldn't run any longer, right. 14 And, you know, you're asking me the same sort of 15 questions. Can I do something here or could 16 someone have done it? And the goal would really 17 be to understand if one carried out a whole host 18 of biochemical processes, whether or not those 19 biochemical processes would have other 20 unexpected consequences and whether or not it 21 would actually disrupt the entire rest of the 22 workflow. 23 Q. Based on your review of the '981 24 process -- excuse me. 25 Based on your review of the '981

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1 patent, do you have an understanding of how the 2 reflex process works? 3 A. Generally, yes. 4 Q. Okay. 5 And can you identify anywhere in the 6 '981 patent where it states that using two tags 7 is inventive? 8 MS. RAYMOND: Objection. Scope. 9 A. So I don't believe Dr. Cooper 10 presents arguments about the inventiveness of 11 the '981 patent. Dr. Cooper presents arguments 12 about obviousness, and I respond to Dr. Cooper's 13 arguments. I didn't provide the analysis of the 14 '981 patent to the extent that I can easily 15 answer your question. 16 Q. Well, leaving aside what's easier, 17 can you provide any other answer to my question 18 beyond that? 19 MS. RAYMOND: Same objections. 20 Q. Given that, I'm going to withdraw the 21 question given the time it's taking. 22 If you could turn to column 13, 23 please. 24 A. Of? 25 Q. Of the '981 patent.	1 MS. RAYMOND: Objection to form. 2 Scope. 3 Q. Let me ask the question again because 4 I'm just asking you what you did. 5 Did you go through the '981 patent to 6 determine where there was an indication that 7 something was nonconventional? 8 MS. RAYMOND: Objection. Form. 9 Scope. 10 A. So as we've discussed numerous times 11 today, my goal in preparing this report and 12 providing this deposition today was not to 13 provide a full analysis of the '981 patent, but 14 to respond to Dr. Cooper's arguments regarding 15 obviousness. 16 So Dr. Cooper cites to three 17 different references in presenting his 18 arguments, but primarily Linnarsson and 19 McCloskey. And so I've done a detailed 20 point-by-point analysis of Dr. Cooper's 21 assertions. 22 I haven't done the type of analysis 23 that you're suggesting. I provide a summary on 24 page 11, 12, 13, 14, 15, 16 and 17 of the '918 25 [sic] patent, and I'd be happy to walk through
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1 A. Sure. 2 All right. I'm there. 3 Q. All right. 4 Do you see where it says, "The 5 practice of the present invention may employ, 6 unless otherwise indicated, conventional 7 techniques and descriptions of organic 8 chemistry, polymer technology, molecular 9 biology...cell biology, biochemistry and 10 immunology, which are within the skill of the 11 art." 12 Do you see that? 13 A. Yes, I do. 14 Q. Okay. 15 And do you understand that the use of 16 tagging the MID, that the cell tag is within the 17 skill of the art as a conventional technique? 18 Let me ask the question this way. 19 Let me step back. 20 Did you analyze whether the '981 21 patent describes particular techniques as 22 otherwise indicated? In other words, did you go 23 through and determine what's otherwise indicated 24 as not being conventional and what's just 25 conventional?	1 that to see if any of what I present here 2 address the question you're asking. 3 Q. All right. 4 Now, with respect to ligation, if you 5 could turn to column 6, please. 6 Do you see where ligation is 7 described from line 15 to 32? 8 A. Yes. 9 Q. And you'll agree that ligation is 10 described in column 6 of the '981 patent is 11 described as a conventional prior art technique? 12 A. So I don't think they use the term -- 13 I don't see the term "conventional" here. But 14 ligation was a method that was well known in the 15 art before the priority date of the '981 patent. 16 Q. Is there anywhere in the '981 patent 17 where it indicates that ligating -- that 18 ligation in terms of generating the tag 19 polynucleotide is not conventional? 20 MS. RAYMOND: Objection. Form. 21 A. So I haven't performed a detailed 22 analysis of the '981 patent with regard to what 23 individual steps may or may not be conventional. 24 I looked at Dr. Cooper's arguments about the 25 '981 patent. Dr. Cooper offers arguments

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1 regarding the obviousness of claim 5 of the '981 2 patent. And claim 5 is the claim, you may 3 recall, that says, "The method of claim 1, 4 wherein the tagged polynucleotides are generated 5 through at least one ligation reaction." 6 So ligation is used. Ligation is a 7 method that was known in the art just like PCR 8 was known in the art. But it's a way of 9 carrying out claim 1. 10 Dr. Cooper doesn't present any 11 arguments about ligation being nonconventional. 12 But Dr. Cooper makes assertions about how one 13 might modify Linnarsson through ligation. And 14 Dr. Cooper's arguments about how that would 15 occur are actually deficient, and I'd be happy 16 to step you through those. I believe they begin 17 on page 51 of my report and run through page 69. 18 Q. Please identify where in the '981 19 patent there's an indication that the use of 20 ligation as specified in dependent claim 5 is 21 not conventional. 22 MS. RAYMOND: Objection. 23 Q. If it's in here. 24 MS. RAYMOND: Objection. Scope. 25 A. So I'm not sure I understand your	1 report is Dr. Cooper's assertion that the tags 2 could be ligated on to the method proposed in 3 Linnarsson and still represent an effective 4 analysis. 5 So the first reason we talked about 6 that not being feasible is the presence of 7 biotin. 8 The second reason that would not be 9 feasible is that Linnarsson describes the use of 10 BTS CL as an enzyme to cut the sequences and 11 release them from the streptavidin beads, and 12 anything that was ligated on outside of the BTS 13 sequence would not have been then present in 14 downstream sequencing. 15 So we can discuss Dr. Cooper's 16 deficiencies and Dr. Cooper's arguments. 17 Whether or not ligation -- I told you earlier 18 ligation was a conventional technique, but, you 19 know, you're asking me different questions about 20 the inventiveness of the patents and 21 Dr. Cooper's arguments. 22 So I wouldn't contest it's well 23 known, but it just wouldn't work with 24 Dr. Cooper's presentation of ligation as a way 25 to represent invalidating prior art in the
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1 question. I haven't done an analysis of the 2 '981 patent with regard to the conventionality 3 of ligation. You'll recall that ligation is 4 used in the dependent claim to carry out -- as 5 one way of carrying out the invention described 6 in claim 1. I'd be happy to look back at the 7 invention in claim 1. But Dr. Cooper doesn't 8 present any arguments about ligation being 9 nonconventional. And so I haven't performed the 10 analysis you're asking me to do now, and I'm not 11 prepared to offer testimony today. 12 Q. If you turn to Cooper report at 239. 13 A. All right. I'm there. 14 Q. Actually, let's just go to 238; it 15 would be easier. 16 A. Okay. 17 Q. Contrary to what you were saying, 18 Dr. Cooper does state that it was well known and 19 routine in the art to attach tag sequences using 20 ligation. 21 Do you see that? 22 MS. RAYMOND: Objection. Foundation. 23 A. So I'm not contesting that ligation 24 was a well-known method of attaching 25 oligonucleotides. What I do contest in my	1 context of modifying Linnarsson and McCloskey. 2 Q. Was it well known and routine in the 3 art to attach tag sequences using ligation in 4 2009? 5 A. It could be but not in the context of 6 modifying Linnarsson in a way that would be 7 functional given Linnarsson's approach. 8 Q. Okay. 9 Leaving aside your arguments, can you 10 say something more than it could be? Was it, in 11 fact -- well, let me see. 12 Dr. Cooper does, in fact, state that 13 it was well known and routine in the art to 14 attach tag sequences using ligation. 15 Do you contest that? It's in 16 paragraph 238 as of the earliest priority date 17 of the '981 patent. 18 A. I don't contest that, but not in the 19 context of modifying Linnarsson. 20 Q. All right. 21 Now, with respect to the dependent 22 claim 5, do you contend that dependent claim 5 23 of the '981 patent, which adds using ligation to 24 generate the tag polynucleotides, do you contend 25 that that's inventive?

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1 MS. RAYMOND: Objection. Scope. 2 Form. 3 A. So I haven't done a thorough analysis 4 of the inventiveness of the '981 patent. My 5 assumption is because the patent issued, that 6 the patent examiner found it to be inventive. 7 If you look at Claim 5, Claim 5 is 8 more than just ligation; it's claim 1 with an 9 additional limitation that ligation is the way 10 that tags are attached. But I am not really in 11 a position today to offer an opinion about a 12 thorough analysis of the inventiveness of the 13 '918 [sic] patent because my assignment and task 14 here in presenting my report and providing my 15 deposition today is to analyze Dr. Cooper's 16 arguments. And Dr. Cooper's arguments about 17 ligating fail for a variety of reasons, which I 18 would be happy to step through with you. 19 Q. Is the addition of the ligation step 20 of claim 5, is that inventive compared to the 21 method of claim 1? 22 MS. RAYMOND: Objection. Scope. 23 Form. 24 Q. I'm just talking about the addition 25 of that ligation step, do you consider that to	1 that? 2 A. I'm sorry, can you point me to where 3 in Dr. Cooper's report? 4 Q. Yes. It's where we just were. 5 Paragraph 236. 6 Do you deny that the applicant didn't 7 identify ligation as an inventive feature when 8 it was arguing for the claims over Linnarsson? 9 MS. RAYMOND: Objection. Scope. 10 A. Dr. Cooper himself does not perform a 11 detailed analysis of the patent prosecution 12 history. He simply says, "I have been informed 13 by counsel that the Patent Owner did not dispute 14 that Linnarsson discloses this limitation during 15 prosecution." 16 So it's hard for me to respond to 17 that without knowing what Dr. Cooper is 18 referring to, other than someone working with 19 him had informed him of that. He doesn't 20 provide any documentary evidence to that. 21 Dr. Cooper doesn't appear to rely on 22 that in presenting his arguments about claim 5. 23 And I'd be happy to step through the places 24 where Dr. Cooper's arguments about ligation are 25 deficient, which are laid out between page 51
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1 be inventive? 2 A. I haven't done a thorough analysis of 3 claim 5 of the '981 patent. I'm happy to 4 discuss the deficiencies in Dr. Cooper's 5 ligation theories with regard to claim 5, but 6 I'm not in a position today to render an opinion 7 about individual inventiveness of individual 8 steps in the patent. 9 Q. Did you consider the file history in 10 preparing your opinions? 11 A. I did, to the extent that it was 12 required for me to respond to Dr. Cooper's 13 arguments about obviousness. And to the best of 14 my recollection, I didn't have to rely on that 15 in presenting the arguments that I'm here to 16 testify about today. 17 Q. Did you review the file history? 18 A. I believe I did, but not in great 19 detail because it wasn't required for me to 20 respond to Dr. Cooper. 21 Q. Dr. Cooper stated that the applicant, 22 when they were trying to identify inventive 23 features of the claims compared to Linnarsson, 24 didn't rely on the ligation step of claim 5. 25 Do you have any reason to dispute	1 and page 59 in my report. 2 Q. When you reviewed the prosecution 3 history in view of Dr. Cooper's statement about 4 how claim 5 was treated during prosecution, did 5 you see anything where the patent owner argued 6 that the ligation of claim 5 was inventive 7 relative to Linnarsson? 8 A. That wasn't the analysis that I 9 performed. It wasn't required to examine 10 Dr. Cooper's assertions that ligation could 11 occur after Step C in Linnarsson's Figure 11. 12 I pointed out reasons why that 13 argument is deficient, including the presence of 14 biotin on both the three prime and five prime 15 ends of the cDNA molecule, and also the fact 16 that if the tag were attached to the five prime 17 fragment end, they wouldn't be sequenced because 18 BTS sequence would leave those behind attached 19 to the streptavidin bead and also because 20 anything attached to the three prime fragment 21 end would also be left behind and attached to 22 the streptavidin bead and therefore not 23 sequenced. 24 So ligation would be a pointless 25 exercise because it wouldn't provide any

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1 information in sequencing. 2 So I didn't have to review the patent 3 prosecution history because Dr. Cooper's 4 arguments are flawed based on the way they're 5 presented in his declaration. 6 MR. REINES: Move to strike 7 everything after "that wasn't the analysis 8 that I performed." 9 Q. And I remind the witness to attempt 10 to be responsive and not to put in nonresponsive 11 argument, because you're now doing that 12 systematically. 13 A. You're asking me about Dr. Cooper's 14 report and so I'm trying to provide context. 15 MR. REINES: The reader can just go 16 up and read the question and answer and 17 evaluate responsiveness for themselves. 18 Q. If you turn to paragraph 40 of the 19 Cooper report. 20 A. All right. 21 (Exhibit 1016 was produced.) 22 Q. And I'll give you Exhibit 1016, which 23 is the supporting documentation. 24 A. All right. 25 Q. And did you review this Exhibit 1016	1 obviousness of the '918 [sic] patent in the 2 context of Linnarsson, McCloskey and Hug, 3 presenting any arguments regarding Exhibit 1016. 4 Dr. Cooper only cites, to the best of 5 my recollection, Exhibit 1016 in discussing 6 prior litigation against the patent owner, 10x 7 Genomics. So given the fact that he didn't 8 offer this as an obviousness argument, I didn't 9 feel that it was necessary for me to review it 10 in detail and cite to it. If I'm mistaken and I 11 did cite to it in my report, I'd ask you to 12 point me to where I did. 13 Q. If you turn to paragraph 40, please, 14 of the Cooper report. 15 A. Okay. 16 I am there. 17 Q. Do you see where it says, "The Patent 18 Owner argued the concept of 'labeling different 19 objects with different labels' is 'as old as the 20 scientific method and is familiar to every 21 student in any introductory science class'..." 22 Do you see that? 23 A. Yes, I see that. 24 Q. Do you have any reason to dispute 25 that?
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1 in preparing your opinions in this case? 2 That should be an easy one. Or 3 explain to me why it's complicated. Let me ask 4 the question again. 5 Did you review Exhibit 1016 in 6 formulating your opinions in this case? 7 A. I don't believe I did. On page 7 of 8 my declaration, I cited the materials I relied 9 upon. I don't list Exhibit 1016, and so I don't 10 recall reviewing it. I may have seen it, but I 11 don't recall it. 12 Q. You referred to what within your 13 declaration? 14 A. So page 7, paragraph 17. There also 15 should have been an Appendix B that was 16 mistakenly left out, but it would have listed 17 the documents. So these are the documents that 18 I cite. I don't believe I cited to Exhibit 19 1016. So if this list is incomplete and I cited 20 to Exhibit 1016 in my declaration, please point 21 me to where I did. 22 Q. And how come you didn't review this 23 document? 24 A. So I don't recall Dr. Cooper, in 25 presenting any of his arguments about the	1 MS. RAYMOND: Objection. Scope. 2 A. So I don't know what context this 3 quote is taken from. I'd be happy to review 4 this document. I'd probably also want to look 5 at the patents that are being discussed to 6 understand the scope and scale of what 7 Dr. Cooper is presenting here. 8 In the context of the analysis I 9 performed, I don't believe Dr. Cooper cited to 10 these in his obviousness arguments; and, 11 therefore, I don't have any context in which to 12 render an opinion about the meaning of this 13 statement. 14 Q. Do you have any basis to dispute 15 Dr. Cooper's analysis in paragraph 42? 16 MS. RAYMOND: Objection. Scope. 17 A. So I don't know what context 18 Dr. Cooper is relying on to make these 19 statements. Again, I haven't reviewed the 20 document you labeled -- or provided labeled 21 Exhibit 1016. I don't believe Dr. Cooper cites 22 to that in his analysis that begins on page 58 23 of his declaration where he states that prior 24 art anticipated or would have rendered obvious 25 the claims of the '981 patent.

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1 So this is out of context for me. I 2 don't believe that he cited to it in those 3 sections, and so I didn't respond to it. If I'm 4 mistaken, you can point me to where I cited to 5 that in my declaration, I'd be happy to refresh 6 my memory. 7 MR. REINES: Why don't we take a 8 break. 9 VIDEOGRAPHER: Off the record at 10 4:09. 11 (Recess.) 12 VIDEOGRAPHER: On the record at 4:25. 13 BY MR. REINES: 14 Q. I'd like to show you the institution 15 decision in this matter. 16 Turn to page 17, please. 17 A. All right. I'm there. 18 Q. And do you see where the decision 19 states, "Patent Owner successfully distinguished 20 Linnarsson during prosecution exclusively on the 21 basis that it does not describe the second tag 22 sequence element which is recited in limitations 23 1F and 1I." 24 A. Yes, I see that. 25 Q. Do you have any reason to disagree	1 at the petition? 2 A. I may have. I don't recall. 3 In response to your earlier question, 4 the PTAB actually does cite to the prosecution 5 history. 6 Q. Could you turn to page 50 of your 7 declaration, please. 8 A. I'm there. 9 Q. And is this the section of your 10 report where you identify why you don't believe 11 there's a reasonable expectation of success in 12 the Linnarsson and McCloskey combination? 13 A. So it's a brief summary. My 14 arguments about Linnarsson and McCloskey in 15 light of claims 1 through 4 and claim 6 being -- 16 or Linnarsson and McCloskey rendering claims 1 17 through 4 and claim 6 obvious are described 18 starting on page 32 and running through page 50. 19 So this is just a brief summary of 20 one of the reasons why -- or some of the reasons 21 why there was no reasonable expectation of 22 success based on Dr. Cooper's arguments. 23 Q. And when you say the one reason that 24 you identify in the reasonable expectation of 25 success section is the issue regarding the
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1 with that? 2 A. I mean, it says that. I mean, I 3 don't know. This is the first time I believe 4 I'm seeing this document. 5 If this is the analysis from the 6 PTAB, I'm assuming the PTAB is correct in its 7 analysis, but I have no basis to render an 8 opinion. 9 Q. And just so if I understand you 10 correctly, you're saying in preparing your 11 response to the petition, you didn't review the 12 PTAB's institution decision regarding that 13 petition? 14 A. Does this have an exhibit number? 15 Q. No. 16 A. No, I don't recall -- I don't recall 17 citing to it. I was responding to Dr. Cooper's 18 arguments, and I don't believe he cited to it 19 either. 20 Q. Do you normally -- let me just ask 21 you again. 22 So you're saying that you didn't 23 review the patent office institution decision 24 when you prepared your response to the IPR 25 petition to understand how the board was looking	1 number of unique tags; is that correct? 2 A. So Dr. Cooper argues that you 3 should -- you need about 100 times more tags 4 than the number of molecules. Dr. Cooper also 5 states in his report that there are 50- to 6 300,000 mRNA molecules per cell, which is the 7 number consistent with what I know is present, 8 which would argue there should be, I think, 9 between 5 million and 30 million independent 10 tags, and McCloskey discloses 16,038 tags, which 11 would be insufficient. So that's one reason why 12 there would be no reasonable expectation of 13 success. 14 Previously I discussed problems 15 with -- I guess later on I discuss, with respect 16 to claim 5, problems with ligation. But I point 17 out other arguments, too, about why these 18 methods wouldn't work as stated. 19 Q. And how did you select the number of 20 unique tag argument as being the only thing to 21 include in the Reasonable Expectation of Success 22 section? How did you pick that one to do it? 23 And try to be as responsive as you can. 24 MS. RAYMOND: I just caution the 25 witness not to reveal substantive

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1 communications with the attorneys. 2 A. So it's the easiest one to 3 understand, right, if, as Dr. Cooper asserts, 4 you need 100 time more tags than molecules, if 5 you have between 50,000 and 300,000 RNA 6 molecules you want to tag, that means you need 7 between 5 million and 30 million tags to be 8 successful. 9 So even if we buy all of the other 10 arguments that Dr. Cooper makes, and we can 11 discuss all the deficiencies in those arguments, 12 even if you buy all of those, you wouldn't be 13 able to uniquely tag each one of the mRNA 14 molecules present in the cell based on 15 Dr. Cooper's own assertions. 16 And so, again, just from a numerical 17 perspective, it's simply the easiest to 18 understand. 19 Q. What is inventive about claim 1 of 20 the '981 patent? 21 MS. RAYMOND: Objection. Scope. 22 A. So to the extent that I'm responding 23 to Dr. Cooper's arguments, claim 1 is not 24 rendered obvious based on the combination of 25 Linnarsson and McCloskey, and, therefore, is at	1 Q. Let's say someone wanted to know and 2 asked you. 3 A. I haven't performed that analysis, so 4 I would be hesitant to render an opinion today 5 since it's outside the scope of my report. 6 MR. REINES: All right. 7 I may be done. So why don't we take 8 a break and check that out. 9 VIDEOGRAPHER: Off the record at 10 4:36. 11 (Recess.) 12 VIDEOGRAPHER: On the record at 4:46. 13 BY MR. REINES: 14 Q. Earlier you referenced the 454 15 sequencer. 16 Do you recall that, just generally? 17 A. Yes, I do. 18 Q. And you're aware of the use of MIDs 19 with the 454 sequencer? 20 MS. RAYMOND: Objection. Form. 21 A. So I'm bad with acronyms. I forget 22 exactly how a MID is defined. 23 Q. Multiplex identifier. 24 A. Multiplex identifier. 25 I believe, I don't recall exactly,
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1 least inventive relative to Linnarsson and 2 McCloskey. Beyond that, I haven't done a 3 detailed analysis of the inventiveness of claim 4 1 because it was outside of the scope of what 5 was necessary to respond to Dr. Cooper. 6 Q. Are you able to describe, based on 7 all of your work on this matter, what you think 8 is inventive about any of the claims in the '981 9 patent? 10 MS. RAYMOND: Objection. Scope. 11 A. I haven't done that analysis, other 12 than to respond to Dr. Cooper's arguments that 13 claim 1 is rendered obvious by the combination 14 of Linnarsson and McCloskey. And I'm happy to 15 describe the reasons why claim 1 is not obvious. 16 Q. Can you answer my question beyond 17 that? 18 MS. RAYMOND: Same objections. 19 A. Would you repeat the question, 20 please? 21 Q. Are you able to describe, based on 22 all your work on this matter, what you think is 23 inventive about any of the claims in the '981 24 patent? 25 MS. RAYMOND: Same objections.	1 but I believe that there were applications on 2 454 that allowed multiplex sequencing, but I 3 don't recall fully. I am much more familiar 4 with the applications on the Illumina sequencer 5 allowing for multiplex sequencing. 6 Q. You're not saying that the '981 7 patent invented MIDs? 8 MS. RAYMOND: Objection. Scope. 9 Q. Well, you were using the term "MID" 10 earlier today. 11 A. So I don't recall the exact context 12 of my comment and so I may have misspoken. 13 A multiplex identifier as defined by 14 the '918 [sic] patent has two specific 15 components. What I was talking about earlier, I 16 believe, when I was talking about the '918 [sic] 17 patent -- or, sorry, when I was talking about 18 the 454 sequencer was the use of multiplex tags 19 so that each individual sample and all the 20 molecules in that sample had a sample-specific 21 tag. So, for example, if I wanted to sequence a 22 mixture of your DNA and my DNA, I could use a 23 tag that represented your DNA and a tag that 24 represented my DNA and we could load them on the 25 same lane in the sequencer and then demultiplex

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1 them. 2 So in the context of multiplex 3 sequencing, at least the Illumina platform, I'm 4 pretty sure the Applied Biosystems platform and 5 I think the 454 platform allowed sample 6 multiplexing, but none of them used a MID as 7 claimed in the '918 [sic] patent that had two 8 separate components. 9 Q. If you could go to the front page of 10 the patent '981. 11 A. All right. 12 Q. Do you have that in front of you? 13 A. Yes, I do. 14 Q. Do you see under "OTHER 15 PUBLICATIONS," it says, "'Using Multiplex 16 Identifier Adaptors for the GS FLX..." 17 Do you see that? 18 A. Yes, I do. 19 Q. Okay. 20 And then you see the URL is a 454 21 publication so-called GS FLX -- 22 A. Yes. 23 Q. -- Technology? 24 Okay. 25 In terms of just the acronym "MID" or	1 And so I may have heard it referred to as a MID. 2 I'm not really sure. 3 Q. So are you saying that you believe 4 that the acronym MID in the '981 patent was 5 coined by the applicants for the '981 patent? 6 MS. RAYMOND: Objection to form. 7 A. I don't know who coined the term. I 8 don't know if the MID referred to in the 454 9 document that you pointed out on the front page 10 of the '918 [sic] patent included all of the 11 elements of the MID that occurred and that are 12 claimed in claim 1 of the '981 patent. I simply 13 don't know. 14 Q. Let me address it this way: Without 15 you agreeing that the term "MID" as used for 16 multiplex identifier to relate to sequencing, 17 whether that's the same MID performing the same 18 functions as the claimed MID, had you heard of 19 the term "MID" used prior to 2009 by people to 20 refer to multiplex identifiers generally? 21 A. I don't recall hearing that term, but 22 whether or not I heard it, it would have been 23 different from what's claimed in the '981 24 patents. 25 Q. Do you know one way or the other
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1 the use of the term "Multiplex Identifier (MID)" 2 that existed before the '981 patent application 3 was filed in 2009, right? 4 MS. RAYMOND: Objection. Form. 5 A. So I don't know how this document 6 uses the term "MID." That document -- I believe 7 that use of MID would probably be limited to 8 just the first element of the MID claimed in the 9 '981 patent, but I'd have to review that 10 document to really understand what type of MID 11 they were referring to. 12 The idea of multiplex sequencing is 13 something that was known, but the MID here has 14 two separate components. And to the best of my 15 knowledge, this second element of the MID, the 16 second tag sequence, wasn't something that was 17 well known. 18 Q. The acronym M-I-D for multiplex 19 identifier, described as MID, you heard that 20 before 2009 in your work in connection with 21 sequencing; is that right? 22 MS. RAYMOND: Objection to form. 23 A. It's not an acronym that I was widely 24 familiar with. People use lots of acronyms. 25 Sometimes different acronyms for the same thing.	1 whether you heard it before then? 2 A. I don't recall. I know I've heard 3 about many multiplex sequencing tags. I don't 4 know if they were referred to as MIDs. 5 Q. All right. Thank you. 6 MS. RAYMOND: We may need a minute. 7 VIDEOGRAPHER: Off the record at 8 4:53. 9 (Off the record.) 10 VIDEOGRAPHER: On the record at 4:57. 11 EXAMINATION BY MS. RAYMOND: 12 Q. Dr. Quackenbush, do you recall being 13 asked a question about whether you opined on 14 whether Linnarsson would benefit from 15 McCloskey's barcodes? 16 A. Yes, I do. 17 Q. Okay. 18 And could you open your report and go 19 to paragraph 72 to 76. 20 A. All right. I'm there. 21 Q. Here, do you address Dr. Cooper's 22 motivation to combine arguments? 23 A. Yes, I do. 24 Q. And do you address Dr. Cooper's 25 amplification bias argument in these paragraphs?

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1 A. Yes, I do. 2 Q. And you also address -- you also 3 address Dr. Cooper's opinions that persons of 4 skill would have been motivated to modify 5 Linnarsson's cell tag to incorporate the 6 functionality of McCloskey's batch-stamp and 7 barcode also in paragraph of 67 to 71 of your 8 report? 9 A. Yes, I address Dr. Cooper's arguments 10 there about modifying the Linnarsson cell tag to 11 include the batch-stamp and the McCloskey 12 barcode. 13 Q. Thank you. 14 Could you please turn to paragraph 53 15 of your report. 16 A. All right. 17 I'm there. 18 Q. And could you read the second 19 sentence. 20 A. So it says, "I reviewed the 21 Institution Decision in connection with this 22 Element and understand the Board interpreted 23 Dr. Cooper's combination as conceptually 24 dividing the nucleotides of Linnarsson's 25 cell-tag into two parts, with one part (six to	1 the other -- any of the other publications cited 2 in the '918 [sic] patent. 3 Q. And I believe you said earlier that 4 everything from one person is tagged with one 5 tag and everything from another person is tagged 6 with a different tag. 7 Did I interpret that correctly? 8 A. So I was discussing multiplex 9 sequencing. And in the common use of multiplex 10 sequencing, one would like to run on the same 11 sequence in the same run samples of different 12 origins. And so multiplex sequencing typically 13 used what we would refer to as multiplex tags so 14 that individual samples from different sources 15 would be tagged with sample-specific barcodes. 16 All right. 17 So that was a practice that was well 18 known in the art. I believe as I stated 19 earlier, I haven't reviewed this document and 20 don't know the scope of the multiplex 21 identifiers that were described in the 454 22 documentation. 23 Q. So if I understand you correctly, the 24 454, to the best of your recollection, tags all 25 the cells from one origin or sample the same way
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1 eight of the nucleotides) being used for the 2 functionality of McCloskey's 'batch-stamp,' 3 which Dr. Cooper asserts is the 'first tag 4 sequence,' and the second part (seven of the 5 nucleotides), being used for the functionality 6 of McCloskey's barcode, relying on Dr. Cooper's 7 Paragraph 192." 8 And then I cite to the institution 9 decision. 10 Q. Do you recall one way or another 11 reviewing that institution decision now? 12 A. I do recall it now, yes. And I cited 13 to it here. 14 Q. Then towards the end of this, after 15 today's exercise, you were asked about a 16 citation to a publication on the face of the 17 '981 patent referring to it, I think, as the 18 454. 19 Do you recall that? 20 A. Yes, I do. 21 Q. Okay. 22 And I believe you said that -- did 23 you review that for the purpose of your opinions 24 here? 25 A. No. I didn't review that or any of	1 and then it tags cells from a different -- an 2 entirely different sample a different way? 3 MR. REINES: Objection. Leading. 4 Lack of foundation. 5 A. So I'm not sure what this document 6 describes, all right. In common parlance, 7 multiplex sequencing refers to running different 8 -- samples of different origin on the same lane 9 of a sequencer. 10 To accomplish that, one used what one 11 would often -- what is commonly referred to as a 12 set of multiplex tags. So we could use a tag 13 for tumor and normal from the same individual 14 and run them -- label all of the molecules from 15 the collection of cells in the tumor and the 16 collection of cells in the normal with one tag 17 in the tumor and a separate tag for the normal, 18 and then run those together, then demultiplex 19 them by detecting the tags. 20 Similarly, I could run a sequence 21 derived from you and a sequence derived from me. 22 All the cells from you would be tagged with one 23 multiplex tag; all of the cells from me would be 24 tagged with another multiplex tags. Those would 25 be run and we could identify the source of

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1 origin either being Megan or John based on the 2 individual multiplex tags. 3 MS. RAYMOND: Thank you. 4 I have no further questions. 5 FURTHER EXAMINATION BY MR. REINES: 6 Q. Just a few follow-ups. 7 In terms of MIDs being used to tag 8 polynucleotides to identify their origin, was 9 there anything specific in the prior art as to, 10 you know, limits on what origins could be 11 designated with the tag? 12 MS. RAYMOND: Objection. It's 13 outside the scope of the redirect. 14 A. So I haven't done that analysis about 15 where particular MIDs might be used. I'm not 16 sure about the use of MID in the context of this 17 document we referred to on the cover of the '918 18 [sic] patent, so I can't really provide an 19 opinion today. 20 Q. When you were responding on 21 cross-examination from 10x regarding MIDs, your 22 testimony was that MIDs could be used to 23 multiplex polynucleotides from different 24 sources, correct? 25 MS. RAYMOND: Objection. Foundation.	1 particular application. Obviously, one couldn't 2 run tens of thousands of samples -- well, there 3 would be some technical barriers to doing that. 4 I don't recall reviewing any 5 documentation that would allow me to provide 6 examples from the prior art on limitations and 7 so I can't do that sitting here today. 8 Q. And then in terms of the other 9 publications, this GS FLX product from Roche for 10 the 454 was a kit of an MID set. You were 11 familiar with the 454. 12 Were you aware that they were selling 13 a product of adaptors that could be used to 14 apply MIDs? 15 MS. RAYMOND: Objection. Outside the 16 scope of the redirect. 17 A. So I don't believe they're actually 18 talking about selling kits. So the GS FLX was, 19 I believe, their sequencing instrument. The 20 titanium chemistry was the chemistry used in 21 that instrument. I don't know what these 22 molecular identifiers were. I don't know if 23 they're being sold. This may be -- this is a 24 technical bulletin that may describe some kind 25 of use of multiplex sequencing. I don't know.
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1 A. So I think you're 2 mischaracterizing -- 3 Q. I don't know if I'm 4 mischaracterizing. Maybe I misunderstood. 5 A. I didn't use the term "MID." I used 6 the term "multiplex tags." I'm not sure how 7 MIDs are being used here. But I described how 8 sample-specific tags could be used in a 9 multiplex sequencing application. And that's 10 what I was referring to in my testimony earlier 11 today about the different sequencing platforms. 12 Q. Okay. 13 Let me try to address that then. 14 In terms of the sample-specific tags 15 for polynucleotides being sequenced, in terms of 16 the origins, they could be designated by the 17 different tag, is there any limits on what could 18 be identified? In other words, you gave the 19 example of two different people; you gave the 20 example of tumor versus non-tumor. Is there any 21 limit in the prior art on what sources could be 22 designated? 23 MS. RAYMOND: Objection. Form. 24 A. So I'm not sure what you're referring 25 to as different sources. It would depend on the	1 I don't have the document to review. And so I 2 can't tell you sitting here today what that 3 document referred to. 4 Q. Do you know what Roche's basic MID 5 set was for its 454 sequencer? 6 MS. RAYMOND: Objection. Outside the 7 scope of redirect. 8 A. I don't have that documentation and 9 so I can't tell you what they were selling 15 10 years ago. 11 MR. REINES: All right. That's it. 12 Thank you. 13 MS. RAYMOND: Thank you. I don't 14 have anything more. 15 VIDEOGRAPHER: Off the record at 16 5:09. This ends today's deposition. 17 MS. RAYMOND: I'll take a rough. 18 19 20 21 22 23 24 25

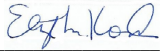
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1 WITNESS'S CERTIFICATION
2
3 _____
4 JOHN QUACKENBUSH, Ph.D.
5
6 On _____, 2024, the foregoing
7 deposition was submitted to JOHN QUACKENBUSH,
8 Ph.D., the witness, taken on Wednesday, February
9 28, 2024, for his examination.
10 At which time the deposition was read by
11 the witness and any proposed changes desired
12 were subsequently entered upon the attached
13 errata sheet.
14 Thereafter, the deposition was duly
15 witnessed and signed by:
16
17 _____
18 Notary Public in and for the
19 County of _____
20 State of _____
21
22
23
24 _____
25 My Commission Expires

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1 E R R A T A S H E E T
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1 C E R T I F I C A T E
2 I, ELIZABETH M. KONDOR, a Certified
3 Court Reporter, License ##30XI00117200, and
4 Notary Public, do hereby certify that prior to
5 the commencement of the examination, JOHN
6 QUACKENBUSH, Ph.D. was duly sworn by me to
7 testify the truth, the whole truth and nothing
8 but the truth.
9 I DO FURTHER CERTIFY that the
10 foregoing is a true and accurate transcript of
11 the testimony as taken stenographically by and
12 before me at the time, place and on the date
13 hereinbefore set forth.
14 I DO FURTHER CERTIFY that I am
15 neither a relative nor employee nor attorney nor
16 counsel of any of the parties to this action,
17 and that I am neither a relative nor employee of
18 such attorney or counsel, and that I am not
19 financially interested in the action.
20
21
22 
23 _____
24 Notary Public
25 Dated: Monday, March 11, 2024