

1 UNITED STATES PATENT AND TRADEMARK OFFICE

2
3 BEFORE THE PATENT TRIAL AND APPEAL BOARD

4
5 PARSE BIOSCIENCES, INC.,

6 Petitioner,

7 v.

8 10X GENOMICS, INC.,

9 Patent Owner.

10
11 IPR2023-00876

12 U.S. Patent No. 10,155,981

13 DEPOSITION OF GREGORY COOPER, PhD

14 Wednesday, December 20, 2023

15 9:56 a.m. EST

16
17
18
19
20 Job No.: 518804

21 Pages 1 - 63

22 Reported by: Karen Klerekoper, CSR-4250, RPR

1 Deposition of GREGORY COOPER, PhD, conducted
2 virtually:
3

4
5 Pursuant to Notice, before Karen Klerekoper,
6 Notary Public in and for the State of Michigan.
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A P P E A R A N C E S

ON BEHALF OF THE PETITIONER, PARSE
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WITNESS:

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GREGORY COOPER, PhD

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5

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Exhibit 1002,

6

Exhibit 1003, Linnarsson

21

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P R O C E E D I N G S

(Oath stipulation read and agreed by counsel
and witness.)

GREGORY COOPER, PhD, having been duly sworn
testified as follows:

EXAMINATION

BY MS. RAYMOND:

Q Dr. Cooper, could you just state your name
for the record, please.

A Sure. My name is Greg Cooper.

Q Thank you. Thanks for joining us this
morning.

And are you the person that wrote an
expert report in IPR2023-00876?

A Yes.

Q Okay.

MS. RAYMOND: And I don't know if the tech
is able to bring up Exhibit 1002 on to the screen.

Great, thank you.

Q And, Dr. Cooper, the report that's being
shown here that has a stamp, if we can scroll down
on the bottom right is Exhibit 1002. Do you see

09:54:41

09:54:41

09:55:05

09:56:14

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09:56:36

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09:56:39

09:56:42

09:56:56

09:56:57

09:56:59

09:57:03

1	that?	09:57:06
2	A I do.	09:57:06
3	(Marked for identification Exhibit 1002,	09:57:07
4	Dr. Cooper's declaration.)	09:57:09
5	Q And you've received a link to the exhibits	09:57:09
6	in this deposition, so you can access this	09:57:12
7	document should you want to open it and look at	09:57:15
8	different parts of it yourself, correct?	09:57:17
9	A Yes.	09:57:19
10	Q Okay. Great.	09:57:19
11	If we could turn to paragraph 13, and that	09:57:21
12	is on page -- little page 5, stamped page 10 of	09:57:26
13	the declaration.	09:57:32
14	A Okay.	09:57:34
15	MS. RAYMOND: If we can keep going. Keep	09:57:48
16	going down. It's actually the end of paragraph 12	09:57:50
17	I would like to look at.	09:57:53
18	Great. Perfect.	09:57:57
19	Q At the end of paragraph 12, Dr. Cooper,	09:57:59
20	you mentioned having extensive experience with a	09:58:02
21	variety of techniques, including single-cell	09:58:05
22	sequencing. Do you see that?	09:58:10

1	A I do.	09:58:11
2	Q Could you tell me what you mean by	09:58:11
3	single-cell sequencing here in this paragraph?	09:58:14
4	A Sure. So, one of my close collaborators	09:58:16
5	is a friend and colleague and my boss, Rick Myers,	09:58:21
6	and his lab does a lot of molecular biology work,	09:58:25
7	especially recently on neurological diseases. And	09:58:31
8	we have collaborated together on a number of	09:58:33
9	projects, including some work over -- especially	09:58:35
10	over the last several years related to the	09:58:37
11	behavior of -- of individual neurons and what gene	09:58:40
12	expression and how regulatory elements of DNA	09:58:44
13	elements inside chromatin regulate gene expression	09:58:47
14	at a single-cell level.	09:58:51
15	Q Okay. So, I understand a little bit that	09:58:52
16	that's your sort of experience with single-cell	09:58:57
17	sequencing. What do you mean by the term or the	09:59:00
18	phrase "single-cell sequencing" in this paragraph?	09:59:02
19	A So, I think it encompasses various kinds	09:59:06
20	of experiments, but essentially it's looking at	09:59:10
21	gene expression and things like open chromatin,	09:59:13
22	so experiments that measure how open or closed a	09:59:17

1	site is that may indicate whether it's regulating	09:59:21
2	a nearby gene.	09:59:23
3	Q If we could now turn to paragraph 73 of	09:59:58
4	your declaration, and that's on original page 32,	10:00:02
5	it's stamped as page 37 on the bottom right.	10:00:07
6	A Okay.	10:00:16
7	Q Okay. Here at the end of that paragraph,	10:00:21
8	which goes on to originally through page 33,	10:00:30
9	stamped page 38, you say that: Traditional	10:00:34
10	techniques rely on bulk analysis.	10:00:40
11	And you go on to say that: Bulk analysis	10:00:42
12	obscures results caused by cells which vary in	10:00:45
13	pathways that are active. Genes that are	10:00:50
14	expressed and functions performed in a cell at any	10:00:53
15	given point in time.	10:00:57
16	Do you see that?	10:00:58
17	A Yes.	10:00:59
18	Q And then you say that, in the next	10:00:59
19	paragraph, paragraph 74: Single-cell genomics	10:01:06
20	allows for the analysis of samples on a	10:01:13
21	single-cell basis.	10:01:15
22	Right?	10:01:17

1	A Yes.	10:01:17
2	Q Okay. When you say "samples" there in	10:01:18
3	paragraph 74, what do you mean by "samples"?	10:01:21
4	A I mean it's -- it's a broad term. It can	10:01:25
5	encompass cells grown in a dish. It can encompass	10:01:29
6	tissue samples from a donor or a patient.	10:01:34
7	It could encompass samples from nonhumans,	10:01:37
8	you know, that you could do single cells on -- on	10:01:41
9	essentially any species. So, it's -- I think it's	10:01:43
10	a broad term.	10:01:46
11	Q And when you say you could do single cells	10:01:47
12	on essentially any species, what do you mean by	10:01:50
13	"do single cells"?	10:01:54
14	A Just, again, the process of looking at the	10:01:56
15	genes that are expressed and the regulatory	10:02:00
16	elements that are active on a -- on a cell-by-cell	10:02:03
17	basis from an input sample, and that sample could	10:02:07
18	come from a variety of sources and organisms.	10:02:10
19	Q And can you explain how performing bulk	10:02:17
20	analysis on a cell differs from single-cell	10:02:22
21	sequencing as you've used it in your report?	10:02:28
22	A Sure. So -- and you say how it obscures,	10:02:32

1	is that what you asked about?	10:02:36
2	Q How performing bulk analysis on a single	10:02:38
3	cell differs from single-cell sequencing as you've	10:02:41
4	used that term in your report?	10:02:45
5	A So did you say bulk analysis of a single	10:02:46
6	cell or just bulk analysis?	10:02:50
7	Q I asked bulk analysis of a single cell.	10:02:52
8	If it's easier, we can start with bulk analysis	10:02:55
9	versus single-cell sequencing generally.	10:02:58
10	A Sure. Okay. Yeah. So -- so, in general	10:03:02
11	bulk analysis is when you have a bunch of cells	10:03:03
12	or, say, a tissue sample and you look at -- you	10:03:06
13	essentially do sequencing readouts of all the	10:03:11
14	cells that are present without any ability to	10:03:14
15	assign the expression or regulatory elements to	10:03:17
16	any one cell. You just are getting the sort of	10:03:20
17	average view across all of the cells.	10:03:22
18	Whereas, in a single cell, you are looking	10:03:26
19	at each cell individually and assigning those	10:03:28
20	functions on a per-cell basis. So, that's kind of	10:03:31
21	the main conceptual difference.	10:03:34
22	Q Okay. So, for single cell, you're getting	10:03:39

1 readouts of all of the cells but on a cell-by-cell 10:03:43
2 basis; is that correct? 10:03:48

3 A Well, you may not be getting all the cells 10:03:49
4 in your sample, but you're -- you're getting 10:03:52
5 information that's pertinent to each cell that 10:03:53
6 you're measuring on a cell-by-cell basis. 10:03:56

7 Q And when you use the term "single-cell 10:03:58
8 genomics" in your report, does it mean doing 10:04:18
9 genomic analysis separately for a bunch of 10:04:21
10 individual cells, or is there some aspect of that 10:04:24
11 single-cell genomics for which the analysis is 10:04:28
12 done for the group of cells? 10:04:34

13 MR. WALTER: Objection, form. 10:04:36

14 A So, I'm not quite sure -- it sounds like 10:04:39
15 you're talking about what can you do with 10:04:42
16 single-cell data, and I think you could imagine 10:04:44
17 performing a variety of tasks, where you look at 10:04:46
18 one cell at a time, or a task where you look at 10:04:49
19 groups of cells that share some property. 10:04:52

20 Q I'll try to explain this a little bit 10:04:55
21 better. I think we see, for example, in 10:04:58
22 Linnarsson, right, where there are cells in a 10:05:01

1 sample that are separated out into, you know, 10:05:05
2 wells with a cell in each well, and then they are 10:05:09
3 combined back again for some additional 10:05:12
4 processing. But you -- you know and you're able 10:05:14
5 to tell, you know, something about one cell versus 10:05:16
6 something about a second cell. 10:05:19

7 And what I'm trying to understand is 10:05:20
8 whether that's something that is an element of 10:05:22
9 single-cell sequencing, or whether, for example, 10:05:27
10 if you just did separate experiments of individual 10:05:29
11 cells in parallel, whether that would also be 10:05:35
12 single-cell genomics in the way that you've used 10:05:39
13 that phrase in your report? 10:05:43

14 MR. WALTER: Objection, form. 10:05:44

15 A So, I -- I guess I'm still not 10:05:46
16 understanding the -- the point of the question. 10:05:49
17 The -- in general, single-cell analyses involve 10:05:51
18 looking at individual cell -- looking at genomic 10:05:54
19 information that is assigned to individual cells. 10:05:58
20 There are various ways to gather that data and 10:06:01
21 various ways to use that data. But single-cell 10:06:04
22 data is fundamentally data that comes from a 10:06:08

1	single cell.	10:06:10
2	Q Okay. So, if I do an experiment on one	10:06:12
3	cell today and an experiment on a second cell	10:06:17
4	tomorrow, would each of those individual	10:06:21
5	experiments be single-cell genomics, in your view?	10:06:27
6	MR. WALTER: Objection, form.	10:06:31
7	A I think it depends on what you're doing.	10:06:32
8	If you're looking at the morphology of that cell,	10:06:35
9	that wouldn't necessarily be genomics. So,	10:06:38
10	I -- again, I -- I don't quite understand that	10:06:42
11	question.	10:06:44
12	Q I think you said in single-cell analysis,	10:06:44
13	looking at genomic information that's assigned to	10:06:51
14	individual cells is what you're doing	10:06:56
15	in single-cell analysis; is that correct?	10:07:00
16	A Yes, that sounds correct.	10:07:03
17	Q Okay. So, if I look at what -- if I have	10:07:05
18	a tissue sample and I look at the genomic	10:07:09
19	information that's assigned to a single cell	10:07:12
20	today, I run one experiment on one cell today, is	10:07:15
21	that single-cell genomics in the way that you've	10:07:19
22	used that phrase in your report?	10:07:23

1	MR. WALTER: Objection, form.	10:07:25
2	A I think it depends on what experiment	10:07:25
3	you're running.	10:07:28
4	Q Okay. Why does it depend?	10:07:29
5	A Well, because, again, if you're	10:07:31
6	looking -- we're using genomics and sequencing, so	10:07:35
7	if you're not doing a sequencing, then you're not	10:07:38
8	doing a single-cell sequencing.	10:07:40
9	If you're not looking at genomic	10:07:43
10	information, then you're not doing genomics.	10:07:45
11	So I think you need to be specific about	10:07:47
12	what experiment you're performing. And -- and I	10:07:49
13	should say that, again, fundamentally what I said	10:07:51
14	when I com -- in my report is that single-cell	10:07:54
15	genomics is when you gather genomic information on	10:07:58
16	a cell-by-cell basis.	10:08:01
17	Q Does single-cell genomics require the	10:08:02
18	gathering of information about more than one cell?	10:08:08
19	A Fundamentally, I -- probably not. I've	10:08:11
20	not thought about that kind of odd edge case. You	10:08:13
21	typically would never do that. But I think single	10:08:18
22	cell would suggest exactly what it sounds like,	10:08:21

1	right? It's -- it's that you're looking at one	10:08:22
2	cell at a time.	10:08:24
3	Q Okay. Could we look at paragraph 75 of	10:08:39
4	your report. That's on the same page we've been	10:08:44
5	looking at. And there, you say: Gene expression	10:08:46
6	analysis in single cells has been widely practiced	10:08:50
7	since the '90s.	10:08:53
8	And you site three references: Brady,	10:08:55
9	Brail and Eberwine.	10:08:57
10	Do you see that?	10:08:59
11	A I do.	10:09:00
12	Q And did you review these references in	10:09:00
13	preparing your report?	10:09:03
14	A I did.	10:09:05
15	Q Okay. Are the techniques described in	10:09:05
16	these references different than the NGS technology	10:09:11
17	described later in paragraph 75 of your report?	10:09:15
18	A At a -- at a high level, of course, there	10:09:20
19	are differences in the technological level that	10:09:23
20	people worked on in the '90s versus what's	10:09:26
21	available certainly today. And over the last ten	10:09:30
22	years, the -- the -- the differences in sequencing	10:09:32

1 are really profound. 10:09:35

2 Q In your opinion, do Brady, Brail and 10:09:37
3 Eberwine describe either single-cell genomics or 10:09:42
4 single-cell sequencing? 10:09:49

5 A I mean, I have to go back and look whether 10:09:50
6 those particular terms would apply. I mean, I 10:09:52
7 think I'm comfortable saying they looked at gene 10:09:56
8 expression at individual cells. Whether you would 10:09:59
9 call that genomics is kind of -- you know, even 10:10:00
10 the phrase "genomics" is a little bit loaded at -- 10:10:04
11 at a conceptual level of what -- you know, there's 10:10:07
12 lots of fun debates you can have about genomics 10:10:10
13 versus genetics that, you know, I'm not going to 10:10:14
14 stick my neck out on anything there to say that 10:10:17
15 that was or was not genomics or genetics per se. 10:10:19

16 But it's -- what I'm comfortable with is 10:10:23
17 what I wrote, which is that they looked at gene 10:10:24
18 expression of single cells. 10:10:25

19 Q Do you recall whether Brady, Brail and 10:10:26
20 Eberwine describe preserving unique information of 10:11:16
21 each cell in a sample of cells? 10:11:19

22 A I don't recall the details of those 10:11:23

1	references right now. It's been quite a while	10:11:26
2	since I looked at those.	10:11:29
3	Q Okay. Those are references 1032, 1006 and	10:11:30
4	1033.	10:11:37
5	Do you have access to those in the link	10:11:38
6	that you were provided?	10:11:42
7	A I do.	10:11:43
8	Q Would you be able to look at those and	10:11:43
9	tell me whether Brady, Brail and Eberwine describe	10:11:46
10	preserving the information in each cell in a	10:11:50
11	sample of cells?	10:11:55
12	MR. WALTER: Objection, form.	10:11:57
13	A Well, so, I mean, if you -- I guess what	10:12:12
14	I'm comfortable saying is what I wrote in my	10:12:15
15	report, which is that they were doing gene	10:12:17
16	expression with resolution down to small numbers	10:12:19
17	of cells or, in some cases, single cells. And so,	10:12:22
18	the rest of the verbiage you used, I'm not	10:12:26
19	necessarily comfortable with that.	10:12:31
20	I'm happy with what I wrote in my report,	10:12:31
21	which is that this is gene expression at the	10:12:34
22	single-cell level.	10:12:38

1	Q Okay. Could you turn to paragraph 92,	10:12:38
2	please. This is on original page 40, stamped	10:13:24
3	page 45.	10:13:27
4	A Did you say 92?	10:13:34
5	Q Yes, paragraph 92, please.	10:13:35
6	A Yes.	10:13:37
7	Q And maybe just backing up. At the end of	10:13:38
8	paragraph 91, you talk about reducing	10:13:44
9	amplification bias.	10:13:48
10	And then at the beginning of paragraph 92,	10:13:49
11	you say: To solve this problem, molecular tags	10:13:50
12	can be added to target sequences prior to the	10:13:53
13	amplification step?	10:13:57
14	Do you see that?	10:13:58
15	A Yes.	10:13:59
16	Q And that's referring to solving the	10:14:00
17	problem of reducing amplification bias, correct?	10:14:02
18	A That's correct.	10:14:05
19	Q Okay. Why is it that adding molecular	10:14:07
20	tags to target sequences prior to the	10:14:11
21	amplification step help to reduce amplification	10:14:14
22	bias?	10:14:20

1 A The -- the main problem of amplification 10:14:20
2 bias is that when you perform -- so, you talk 10:14:26
3 about PCR as the -- the -- you know, a dominant 10:14:28
4 form of amplification, the common form, at 10:14:31
5 least -- is that it can affect certain templates 10:14:34
6 differentially. So, some templates -- the one 10:14:39
7 example is that a very large template will get 10:14:41
8 amplified more slowly than very small templates, 10:14:46
9 all else being equal. 10:14:50

10 And so, if you have a reaction where you 10:14:52
11 have different sizes, because it's an exponential 10:14:53
12 growth of -- it's -- amplification is an 10:14:56
13 exponential growth process, that even small 10:14:59
14 differences in the efficiency of amplifying one 10:15:01
15 template versus another will lead to huge 10:15:04
16 differences -- orders of magnitude differences in 10:15:07
17 the numbers of molecules of -- in the numbers of 10:15:10
18 copies of one template versus another, even if 10:15:14
19 they started out at the same concentration in the 10:15:16
20 input. 10:15:19

21 And so, that's fundamentally the problem 10:15:20
22 with amplification bias is that you can't control 10:15:22

1 the intrinsic efficiency of PCR of any given 10:15:25
2 template. 10:15:30

3 And so, tagging -- what tagging allows you 10:15:30
4 to do is you put a tag on each template before you 10:15:33
5 make a bunch of copies. And then at the end, you 10:15:37
6 can count the redundancy of that tag and say, 10:15:40
7 well, I know that each -- that -- that -- to the 10:15:43
8 extent that those tags are identical from the 10:15:45
9 actual end stage readout, you know that they were 10:15:47
10 all derived from one input template, regardless of 10:15:50
11 how many copies you detect at the end of the 10:15:53
12 experiment. 10:15:56

13 Q So, adding a tag after the amplification 10:15:57
14 step would not reduce the amplification bias. You 10:16:02
15 would have to add it before the amplification; is 10:16:04
16 that correct? 10:16:07

17 A So, the -- as a general rule, the earlier 10:16:07
18 you add it, the more effective that tag will be. 10:16:10
19 You know, I think you could imagine a scenario 10:16:14
20 where tags after, say, two or three rounds would 10:16:15
21 still be better after 20 rounds. But, yes, the 10:16:18
22 ideal experiment is that you tag it before you 10:16:22

1 perform cycles of PCR. 10:16:24

2 Q Okay. So, if we could, I would like to 10:16:28
3 turn a little bit to your reliance on Linnarsson, 10:16:44
4 which is -- use your report a little bit, too, or 10:16:49
5 certainly you can reference your report, but 10:16:54
6 Linnarsson is Exhibit 1003. 10:16:56

7 (Marked for identification Exhibit 1003, 10:17:00
8 Linnarsson.) 10:16:56

9 Q And I'll just perhaps say to you, if you 10:17:01
10 want to look, it looks like you rely on 10:17:05
11 Linnarsson's disclosure in figure 11 throughout 10:17:09
12 your report. For example, I see it cited in -- I 10:17:12
13 don't know if you want to look -- paragraphs 110, 10:17:17
14 113, 117, 139 to 140, going through 166, at least, 10:17:19
15 of your report. 10:17:27

16 Does that sound right? 10:17:27

17 MR. WALTER: Objection, form. 10:17:29

18 A Yes, I recall figure 11, citing to it a 10:17:31
19 number of times in the report, yes. 10:17:35

20 Q Okay. 10:17:36

21 MS. RAYMOND: And if we could maybe pull 10:17:37
22 up on the screen Exhibit 1003. And particularly 10:17:41

1	on figure 11, which is on stamped page 60, just so	10:17:48
2	we can have figure 11 in front of us.	10:17:54
3	Q And, Dr. Cooper, you recall this figure?	10:18:05
4	A Yes, I do.	10:18:12
5	Q And is this a representation of	10:18:13
6	Linnarsson's method of using CDS and TSOs to tag	10:18:18
7	mRNA in cells?	10:18:24
8	A So, this certainly has elements of the	10:18:27
9	overall Linnarsson process. Obviously, there is a	10:18:32
10	lot more disclosure within Linnarsson, but	10:18:34
11	certainly this has some of the -- the key steps in	10:18:36
12	it.	10:18:39
13	Q Great.	10:18:40
14	I would like to walk through those steps.	10:18:42
15	But first, maybe I can ask you, are you familiar	10:18:46
16	with Linnarsson's reference to an STRT method?	10:18:50
17	A That is ringing a bell, but I can't recall	10:18:58
18	the details of that that particular acronym.	10:19:03
19	Q I'm going to try to find it for you. I'm	10:19:07
20	just having a little bit of a lag on my laptop	10:19:21
21	today.	10:19:25
22	A Okay. I see it. Single-cell tagged	10:19:25

1	reverse transcription method.	10:19:27
2	Q Yes.	10:19:29
3	A Yes, okay.	10:19:30
4	Q And is figure 11, does that show the STRT	10:19:32
5	method?	10:19:39
6	MR. WALTER: Objection, form.	10:19:40
7	A So the -- the title of figure 11 is that	10:19:41
8	it shows a graphical representation of steps	10:19:45
9	optionally used in the STRT method. So, again, I	10:19:49
10	think figure 11 includes some of the key elements	10:19:52
11	of Linnarsson, but certainly not all. And I -- I	10:19:55
12	don't think it's fair to call it the STR method,	10:19:58
13	because it's -- you know, they're describing it as	10:20:03
14	optional steps that can be used within STRT.	10:20:06
15	Q And so, you rely on these steps and others	10:20:09
16	described in Linnarsson in coming to your opinions	10:20:11
17	about Linnarsson; is that correct?	10:20:13
18	A Correct. I use some of the -- you know,	10:20:16
19	figure 11 is part of the evidence of -- of all of	10:20:19
20	the disclosure that's in Linnarsson, yes.	10:20:21
21	Q Okay. If we can just step through A	10:20:23
22	through F of figure 11. What does figure A show	10:20:31

1	within figure 11?	10:20:36
2	A So, in figure 11A, they are showing the	10:20:37
3	input mRNA, sort of that's the top row of that	10:20:46
4	image with five -- five prime to three prime and	10:20:54
5	the poly-A tail at the end. And to that they are	10:20:57
6	hybridizing a primer, an oligonucleotide. That's	10:21:00
7	the PR and the series of Ts. So, the Ts are	10:21:06
8	complementary to the As, and that allows it to --	10:21:08
9	to hybridize or stick to the poly-A tail of the	10:21:11
10	mRNA.	10:21:13
11	And this is sort of the reverse	10:21:13
12	transcription step, where the RT enzyme is adding	10:21:15
13	DNA nucleotides that are a complement of the mRNA	10:21:20
14	input.	10:21:24
15	Q And so, the right side of the bottom tag,	10:21:25
16	that's the CDS; is that correct?	10:21:30
17	A Yeah, I don't believe it's labeled that in	10:21:33
18	this figure, but I think it is. Yes, that is --	10:21:36
19	that is one -- one version of a CDS, correct.	10:21:38
20	Q Okay. And you rely on this version of the	10:21:40
21	CDS for your opinion, correct?	10:21:43
22	A It's -- it's certainly one of -- right,	10:21:46

1 there are other figures that we talk about -- you 10:21:48
2 know, there's text about the CDS. Figure 2 talks 10:21:50
3 about, you know, there are other examples and 10:21:55
4 representations of it, but this is certainly part 10:21:56
5 of the evidence. 10:21:59

6 Q And so, you rely on this example of this 10:22:00
7 CDS and perhaps others for informing your opinion? 10:22:04

8 A Correct. This is one example of multiple 10:22:10
9 that are talked about in my report. 10:22:12

10 Q And on the far right side of figure A, the 10:22:14
11 bottom strand, I see a BIO. Do you see that? 10:22:25

12 A I. 10:22:28

13 Q What is that? 10:22:29

14 A I believe that is a molecule called 10:22:30
15 biotin, which is useful for a downstream step 10:22:35
16 to -- to essentially separate out your molecules 10:22:37
17 to clean them up. 10:22:40

18 Q Okay. Is that part of the CDS? 10:22:42

19 A In this particular case, they are 10:22:45
20 showing -- you know, they are showing an example 10:22:47
21 where these primers are biotin related, yes. 10:22:49

22 Q Okay. And then, moving on to step B here, 10:22:52

1	can you describe to me what figure 11B shows?	10:23:02
2	A So, in 11B -- so I want to import the	10:23:07
3	point we forgot with A is that when the RT enzyme	10:23:16
4	hits the end of the -- the five prime end of the	10:23:18
5	RNA, it naturally adds a few Cs, so a few	10:23:23
6	cytosines.	
7	So, in step B, the process takes advantage	10:23:27
8	of those nontemplated Cs, and you have a primer	10:23:29
9	that they call a template switching	10:23:32
10	oligonucleotide, or that's what it's called, that	10:23:37
11	uses Gs at the end so that it can anneal to the	10:23:39
12	Cs.	10:23:41
13	And then you use that primer to then	10:23:42
14	initiate an extension reaction that can complete	10:23:45
15	the second strand of a double-stranded cDNA.	10:23:49
16	Q Okay. So, the top strand in figure B, is	10:23:53
17	that showing the second strand of cDNA being	10:24:04
18	formed, or is that the original strand of the mRNA	10:24:10
19	with the TSO added?	10:24:15
20	A So it's a little bit unclear since they	10:24:17
21	didn't label it super crisply. But if you read	10:24:19
22	the -- the legend, it describes it as panel B as	10:24:24

1	the template switching step, and that, you know,	10:24:26
2	it says: As a consequence, the three prime end of	10:24:29
3	the cDNA will carry a barcode XXXX.	10:24:32
4	And whether there -- I'm trying to	10:24:36
5	remember panel C then might help...	10:24:39
6	So, I believe they are showing that that	10:24:43
7	is -- it's a little unclear to me whether that's	10:24:48
8	showing the DNA/RNA hybrid or whether that's a	10:24:51
9	duplex DNA at that point. But at some point,	10:24:54
10	you're making a double-stranded DNA that is the --	10:24:57
11	you know, that carries the copy of the mRNA that	10:24:59
12	was in the input sample.	10:25:03
13	Q Okay. Thank you.	10:25:04
14	Then, have we talked about everything	10:25:07
15	that's shown in figure 11B?	10:25:09
16	MR. WALTER: Objection, form.	10:25:15
17	A So, the -- the other thing that's in the	10:25:17
18	figure legend is that they have this BTS	10:25:20
19	recognition site, but it's -- that's part of how	10:25:23
20	they are going to clean things up later on.	10:25:25
21	Q And the BTS recognition site is part of	10:25:27
22	the TSO in figure 11B?	10:25:33

1	A Yes.	10:25:35
2	Q And you rely on figure 11B in forming your	10:25:36
3	opinion that Linnarsson, in view of McCloskey,	10:25:46
4	renders obvious the claims in the patent, correct?	10:25:49
5	A I rely upon this in addition to other --	10:25:52
6	this is, again, one example of a process that	10:25:54
7	Linnarsson discloses. It's not necessarily all of	10:25:56
8	them. And, again, so we go back to the -- it's a	10:25:59
9	series of optional steps, as they describe it.	10:26:02
10	It's -- it's sort of one embodiment of -- of a	10:26:05
11	universe of disclosures within Linnarsson, yes.	10:26:07
12	Q But you rely on figure 11B in your report,	10:26:10
13	right?	10:26:14
14	MR. WALTER: Objection, form.	10:26:14
15	A In addition to other figures, yes.	10:26:15
16	Q Okay. And then the next step shown in	10:26:17
17	figure 11 is figure 11C, right?	10:26:23
18	A Correct.	10:26:30
19	Q And can you please tell me, what does	10:26:31
20	figure 11C show?	10:26:35
21	A So, this is beginning a -- a -- this sort	10:26:38
22	of the initial PCR step, and that you use primers	10:26:44

1 to -- to amplify the CD -- you know, you make the 10:26:48
2 initial cDNA, and then you attach these primers at 10:26:54
3 the end that allows you to subsequently send it on 10:26:57
4 to PCR to -- to amplify it. 10:27:00

5 Q And then you rely on this 11C in forming 10:27:05
6 your opinions; is that correct? 10:27:11

7 A As -- as one example, yes. 10:27:13

8 Q And then moving on to figure 11D, could 10:27:16
9 you please tell me what figure 11D shows? 10:27:20

10 A So, in 11D, they are cutting the -- 10:27:25
11 they're -- what they call fragmentation. So, 10:27:31
12 they're cutting the amplified copies into smaller 10:27:33
13 pieces. 10:27:38

14 Q Okay. And is that part of Linnarsson's 10:27:38
15 methods that you rely on in making your 10:27:51
16 conclusions regarding grounds one and grounds two 10:27:55
17 and obviousness? 10:27:58

18 A So, again, I cited the figure 11. I don't 10:28:01
19 know that I ever mapped a specific fragmentation 10:28:04
20 step disclosed here on any particular claim 10:28:08
21 elements of the '981, so I don't know that I 10:28:11
22 relied on it per se. But, again, this is one 10:28:13

1 example of an embodiment that I relied upon in my 10:28:17
2 report. 10:28:21

3 Q Is fragmentation part of Linnarsson's 10:28:21
4 method that you rely on in forming your opinions 10:28:23
5 about obviousness? 10:28:25

6 A Well, fragmentation is one optional step 10:28:28
7 that, again, I don't -- I don't recall relying on 10:28:32
8 that particular step as being a necessary part of 10:28:34
9 any individual element of -- of the '981 claims, 10:28:38
10 but it is certainly part of the disclosure of 10:28:40
11 Linnarsson as an optional step within their 10:28:44
12 process. 10:28:47

13 Q You would agree with me that subsequent 10:28:47
14 steps involve sequencing, right? 10:28:49

15 A Within Linnarsson? 10:28:52

16 Q Within Linnarsson, yes. 10:28:54

17 A Yes, absolutely. That -- sequencing is 10:28:55
18 their readout, yes. 10:28:58

19 Q Okay. And is it your position that the 10:29:00
20 sequence polynucleotides in Linnarsson are 10:29:05
21 fragmented? 10:29:14

22 A Not necessarily always, no. 10:29:16

1 Q Okay. Where do you discuss that in your 10:29:20
2 report? 10:29:22

3 A I don't recall discussing it one way or 10:29:24
4 another. Again, I -- this is -- figure 11 is, as 10:29:27
5 they describe it, a series of optional steps that 10:29:30
6 can be used. And part of them are disclosing 10:29:32
7 elements that are pertinent to the '981. But I 10:29:35
8 don't recall ever rendering an opinion as to 10:29:38
9 whether fragmentation per se using DNase was 10:29:40
10 necessary or -- or -- or not necessary for any 10:29:44
11 particular step. 10:29:46

12 Q Then if we could go on to figure 11E. 10:29:55
13 What does figure 11E show? 10:30:01

14 A So, in -- in E, they are showing the -- 10:30:03
15 basically a step that -- that they're using to 10:30:08
16 sort of clean up the products that they would like 10:30:11
17 to sequence and separate them out from other 10:30:14
18 things. So, they're -- they're taking advantage 10:30:16
19 of their cut sites and the beads that are 10:30:18
20 connected to the biotin labels to help clean up 10:30:23
21 what they -- to essentially get a more pure sample 10:30:27
22 to put on a sequencer. 10:30:29

1	Q Do you rely on step E in forming your	10:30:31
2	opinions about Linnarsson and obviousness?	10:30:34
3	A I don't recall mapping step E per se to	10:30:38
4	any claim element of '981, but to the extent that	10:30:41
5	it's part of figure 11, it's certainly part of a	10:30:43
6	disclosure of Linnarsson that I looked at.	10:30:48
7	Q And if you could describe for me what's	10:30:50
8	shown in figure F, please, 11F?	10:30:56
9	A In figure F, they're showing essentially	10:30:59
10	that at the end of the result, they -- they	10:31:02
11	released the molecules that then actually get put	10:31:05
12	onto a sequencer that are ligated to adapters that	10:31:08
13	allow them to read out the content on a -- on a --	10:31:12
14	on a high throughput sequencer.	10:31:17
15	Q Okay. If we could -- we might go back to	10:31:32
16	Linnarsson. But for now, if we could take a look	10:31:36
17	at McCloskey, which is Exhibit 1004.	10:31:41
18	(Marked for identification Exhibit 1004,	10:31:44
19	McCloskey.)	10:31:41
20	A Okay.	10:31:55
21	Q And on stamped page 5, and we can pull	10:31:56
22	that up on the screen, but, Dr. Cooper, I assume	10:32:11

1	that you've pulled that up however you see fit.	10:32:14
2	A Yeah, I have --	10:32:18
3	Q Okay. Do you see here, a few lines down,	10:32:18
4	there is a reference to: Human genomic DNA 2.71	10:32:26
5	micrograms was cleaved with 10F1.	10:32:34
6	Is that right?	10:32:38
7	A Yes, I see that.	10:32:39
8	Q Okay. So, does McCloskey disclose tagging	10:32:40
9	2.71 micrograms of DNA in its sample?	10:32:58
10	A Well, in this case, they're not -- they	10:33:07
11	are digesting 2.71 micrograms in this particular	10:33:12
12	experimental description.	10:33:16
13	Q Okay. And then is that 2.71 micrograms	10:33:17
14	tagged in this description?	10:33:20
15	A Well, it's -- I mean, it's at that step	10:33:25
16	it's digested.	10:33:28
17	Q Okay.	
18	A And then eventually it goes through a	10:33:30
19	process which includes adding oligos that anneal	10:33:33
20	to it.	10:33:37
21	Q Okay. And sorry, I think I may have	10:33:37
22	misspoken. It looks like that after the 2.71	10:33:58

1	micrograms of human genomic DNA is cleaved, then	10:34:07
2	.27 micrograms of digested DNA is mixed with	10:34:23
3	sequenase buffer; is that right?	10:34:28
4	(Indiscernible crosstalk.)	10:34:32
5	THE WITNESS: Sorry, go ahead.	10:34:33
6	MR. WALTER: Objection, form.	10:34:34
7	A So, yeah, as, again, I -- they started	10:34:35
8	with 2.7 micrograms in this particular experiment.	10:34:38
9	And when you digest, you generally lose materials	10:34:41
10	in your input. So, they ended up with, in this	10:34:44
11	case, about 90 percent less that actually gets put	10:34:47
12	forward into subsequent reactions.	10:34:51
13	Q And then the encoding oligonucleotide is	10:34:53
14	annealed to that .27 micrograms of DNA?	10:34:58
15	A Well, there's a couple of steps before	10:35:08
16	that, but they do the self-annealing step and	10:35:09
17	then -- but, yes, they are mixing in ultimately	10:35:13
18	that digested genomic DNA with their oligos.	10:35:14
19	Q Do you happen to know how many cells worth	10:35:20
20	of genetic material is reflected in 2.71	10:35:24
21	micrograms of DNA?	10:35:28
22	A I couldn't do that off the top of my head,	10:35:31

1	no.	10:35:34
2	Q Okay. Would it be more than one cell?	10:35:34
3	A Yes.	10:35:36
4	Q Okay. And the encoding oligonucleotides	10:35:37
5	that are added to what's originally 2.71	10:35:50
6	micrograms of DNA, then digested to get down to	10:35:54
7	.27 micrograms of DNA, those encoding	10:35:57
8	oligonucleotides have the same batch stamp; is	10:36:04
9	that correct?	10:36:09
10	A I -- I don't think it specifies. But in	10:36:09
11	general, the McCloskey batch stamp is designed to	10:36:12
12	be consistent across one experiment, so I would	10:36:15
13	imagine. So, but I don't recall the details, if	10:36:19
14	they -- I don't know if they disclosed exact	10:36:21
15	sequence of that oligo, but -- but, yes, in	10:36:23
16	general, a batch stamp would be across a -- one	10:36:28
17	whole experiment --	10:36:32
18	Q And --	
19	A -- or one whole run of an experiment.	10:36:32
20	Q And then the encoding oligonucleotide of	10:36:34
21	McCloskey, is that designed to anneal to alleles	10:36:42
22	for a particular gene in a sample?	10:36:47

1	A So, in general, the McCloskey method is	10:36:50
2	talking about hybridizing to specific -- well,	10:36:56
3	taking advantage of complementarity between your	10:37:00
4	primer and a target template. So, it is designed	10:37:04
5	to go after a set of target templates that are	10:37:07
6	present, and, in this case, in the genomic DNA.	10:37:10
7	Although, again, I would say McCloskey's	10:37:13
8	methods, to the extent that they are talking about	10:37:16
9	methods to design primers for PCR, are very	10:37:18
10	clearly generalizable to a whole range of	10:37:21
11	templates.	10:37:26
12	Q And in your report, do you discuss --	10:37:34
13	where do you -- where do you discuss the idea that	10:37:41
14	McCloskey's methods are very clearly generalizable	10:37:46
15	to a whole range of templates?	10:37:53
16	A So -- well, I mean, it's -- it's -- I	10:37:57
17	can't recall sitting here. But that's, in	10:38:00
18	general, if you look at the -- for example, the	10:38:03
19	abstract of McCloskey mentions -- let's see here,	10:38:05
20	yeah, batch stamp specified a date and sample	10:38:13
21	identity, and bar codes detect template	10:38:18
22	redundancy. So, it's intrinsic to McCloskey.	10:38:21

1 It's talking about PCR products in general. 10:38:24

2 And it talks the problem of amplification 10:38:27

3 bias as a function of template diversity -- or as 10:39:04

4 a function of template redundancy, sorry. So, 10:38:34

5 it's -- the -- you know, the paper is very clearly 10:38:34

6 written as a generalizable -- generalizable way to 10:38:36

7 implement PCR primer design. 10:38:41

8 Q Can you point me to any paragraphs of your 10:38:43

9 report addressing that? 10:38:46

10 A So, in paragraph -- let's see here, I 10:38:51

11 believe if you look at -- I have a whole section 10:38:55

12 on amplification bias that starts at paragraph 90 10:38:57

13 and continues through -- let's see here, 90 -- 10:39:05

14 through the end of paragraph 93. 10:39:15

15 Q Okay. 10:39:23

16 A And there are other references in there, 10:39:25

17 as well, like the Miner reference, but -- but that 10:39:27

18 paragraph discusses the problem of amplification 10:39:30

19 bias in general terms and how that applies to PCR. 10:39:33

20 Q Okay. If we could go back to McCloskey 10:39:36

21 and -- 10:40:07

22 A I'm sorry, and I just -- there are 10:40:07

1 other -- so, in paragraphs 101, 102, and 103 talks 10:40:09
2 about contamination. So, yes, paragraphs 101 10:40:21
3 through 104 also talk about information from 10:40:26
4 McCloskey. 10:40:29

5 Sorry to interrupt. 10:40:29

6 Q Okay. Now, look at McCloskey and your 10:40:46
7 report. On your report, I'm looking at 10:40:52
8 paragraph 176, which talks about McCloskey, I 10:40:55
9 believe. And it says: The batch stamp specifies 10:41:03
10 the DNA source, such as the patient or sample 10:41:06
11 identification. And the sample may be a single 10:41:10
12 "cell sample." 10:41:12

13 And then you cite McCloskey at 762, which 10:41:13
14 is stamped page 2. 10:41:16

15 A Okay. 10:41:18

16 Q Do you see that? 10:41:18

17 A I do. 10:41:19

18 Q And if we go to McCloskey, to that page in 10:41:21
19 McCloskey, and here I am looking for the term 10:41:28
20 "single-cell sample." 10:41:39

21 And I -- I think the -- the place that I 10:41:43
22 see it and the only place on this page is the 10:41:45

1	first full paragraph that starts: We recently	10:41:48
2	addressed.	10:41:51
3	And then goes on and says -- talks about:	10:41:53
4	Irreplaceable or single cell samples and cites	10:41:56
5	Miner, Laird and Lee.	10:42:00
6	Do you see that?	10:42:03
7	A I do.	10:42:03
8	Q Is that what you were referring to in	10:42:04
9	paragraph 176 when you were talking about a	10:42:09
10	single-cell sample in quotes?	10:42:11
11	A I believe so, because I think, yeah,	10:42:14
12	that's page 762. So, I think certainly this is a	10:42:17
13	specific example of McCloskey recommending its --	10:42:21
14	you know, discussing its method being useful for	10:42:25
15	looking at single-cell --	10:42:27
16	Q Okay.	10:42:28
17	A -- data.	10:42:29
18	Q And then did you review the Miner, Laird	10:42:29
19	and Lee references that are cited there in forming	10:42:35
20	your opinions?	10:42:39
21	A I don't recall. I don't -- I know I -- I	10:42:41
22	reviewed those. I don't remember if I	10:42:43

1 specifically -- certainly, they're not -- I didn't 10:42:46
2 rely upon them as grounds for a specific 10:42:48
3 obviousness combination or anything, but I -- I 10:42:51
4 certainly -- I -- I believe they might be exhibits 10:42:53
5 in my report, but I don't remember exactly if they 10:42:56
6 were or not. 10:42:58

7 Sorry. So, for Miner, for example, it's 10:43:27
8 Exhibit 1013 in my report. 10:43:29

9 Q Uh-huh. 10:43:31

10 Okay. And do you recall whether Miner, 10:43:33
11 Laird and/or Lee describe analyzing a sample of 10:43:53
12 multiple cells while providing information on a 10:43:58
13 cell-by-cell basis? 10:44:01

14 MR. WALTER: Objection, form. 10:44:02

15 A I -- I don't remember the details of 10:44:04
16 those. I -- you know, that -- we're generally 10:44:07
17 focused on the template -- template redundancy and 10:44:09
18 amplification bias portion there, but I -- I don't 10:44:16
19 remember all the details of those three 10:44:17
20 references. 10:44:19

21 Q And when you say you were generally 10:44:20
22 focused on the template redundancy and 10:44:26

1 amplification bias portion there, what do you mean 10:44:28
2 by that? 10:44:29

3 A That -- that is the -- the teaching of 10:44:30
4 McCloskey that was particularly relevant is the 10:44:35
5 use of that molecular identifier, that tag that 10:44:38
6 keeps track of input templates as you put them 10:44:42
7 through an amplification process and allows you 10:44:47
8 to -- to essentially solve the -- the problem of 10:44:49
9 uneven PCR amplification bias. 10:44:52

10 Q If we could turn now to paragraph 198 of 10:44:56
11 your report, and that's on original page 94, 10:45:05
12 stamped page 99. And that goes on to the next 10:45:08
13 page. 10:45:17

14 I see here a citation and a block quote to 10:45:17
15 Linnarsson 21:13 to 25. 10:45:24

16 Do you see that? 10:45:29

17 A Wait. So, I see -- I see paragraph 198, 10:45:33
18 and then I see 19:28 to 32; is that what you said? 10:45:37

19 Q I'm actually looking at the next block 10:45:43
20 quote -- 10:45:45

21 A Oh, I'm sorry.

22 Q -- which you cite as 21:13 to 25. 10:45:46

1	A Yes, I see that.	10:45:49
2	Q Okay. Maybe on the screen we can maybe	10:45:50
3	sort of split the screen across the two pages to	10:45:55
4	see more of the quote.	10:45:58
5	And this second quote refers to: The cDNA	10:45:59
6	library can be processed by fragmenting the cDNA	10:46:10
7	library to obtain short fragment five prime end	10:46:14
8	library.	10:46:17
9	Do you see that?	10:46:18
10	A Yes.	10:46:20
11	Q Okay. We were talking about figure 11D	10:46:21
12	earlier. Is that consistent with what we were	10:46:26
13	looking at in figure 11D?	10:46:29
14	MR. WALTER: Objection, form.	10:46:31
15	A So, I don't think they cite figure 11	10:46:32
16	there, but, in general, the -- the -- you know,	10:46:36
17	one of the -- well, certainly when Linnarsson was	10:46:39
18	published, the dominant forms of high throughput	10:46:44
19	sequencing could only generate between, you know,	10:46:47
20	1 and 300 base pair fragments of information.	10:46:50
21	And so, you -- you -- at some point, you	10:46:53
22	would need to -- you can't put huge molecules on	10:46:55

1	there. So, at some point, you need to fragment to	10:46:58
2	get them -- to make them suitable for the	10:47:01
3	particular sequencer machine that you're using.	10:47:03
4	Q And with respect to this quote that we	10:47:07
5	were just looking at, in your opinion, is that the	10:47:13
6	same embodiment of Linnarsson as is shown in	10:47:15
7	figure 11D or a different embodiment?	10:47:18
8	MR. WALTER: Objection, form.	10:47:21
9	A I -- I think they're -- again, I think	10:47:22
10	they're in general relevant to the concept of	10:47:25
11	preparing fragments to -- preparing the thing that	10:47:28
12	you -- the cDNA molecules that you prepared to	10:47:32
13	making them suitable for sequencing on a	10:47:35
14	particular sequencing platform.	10:47:38
15	I -- again, I don't know specifically if	10:47:39
16	they're -- if figure 11 is exactly what they're	10:47:42
17	disclosing there. But certainly, they're related	10:47:45
18	to the same concept of preparing fragments to make	10:47:48
19	them suitable for sequencing on a high throughput	10:47:52
20	sequencer.	10:47:56
21	Q And are you aware of any disclosure in	10:47:56
22	Linnarsson describing obtaining a short fragment	10:48:26

1	three prime end library?	10:48:33
2	A I don't recall that. Yeah, I don't -- I	10:48:36
3	don't think I cite it in my report, if I did. But	10:48:45
4	I -- yeah, it may have, but I don't remember.	10:48:49
5	Q Okay. And do you know whether Linnarsson	10:48:51
6	states that the three prime fragment is released	10:48:54
7	from the bead?	10:48:58
8	A Specifically with respect to figure 11?	10:49:04
9	Q With respect to figure 11 or anywhere else	10:49:08
10	in Linnarsson that you've -- anywhere else in	10:49:10
11	Linnarsson.	10:49:15
12	A Yeah, I'm not remembering. I think in	10:49:16
13	that figure 11, the legend says that it's the	10:49:27
14	three prime fragments remains stuck on the beads.	10:49:29
15	But, again, whether there was another	10:49:33
16	disclosure, I just -- I'm not recalling.	10:49:35
17	Q You don't recall citing anything in	10:49:38
18	Linnarsson that states that the three prime	10:49:40
19	fragment is released from the bead; is that	10:49:43
20	correct?	10:49:45
21	A That -- that's right. I don't remember	10:49:45
22	doing that.	10:49:47

1	Q And if we can move on to ground 2. And,	10:49:49
2	Dr. Cooper, just if at any point you want a break,	10:49:58
3	please just let me know and we'll take a break.	10:50:02
4	A Okay.	
5	Q I'm trying to get through this quickly,	10:50:05
6	but we'll take whatever breaks are convenient to	10:50:07
7	you.	10:50:10
8	A Maybe another half-hour or something	10:50:11
9	and -- yeah.	10:50:16
10	Q Okay. Moving on to ground 2, your	10:50:16
11	ground 2 opinion -- let me bring us, perhaps, to	10:50:19
12	the right section, at least. That's on page 108,	10:50:30
13	I believe. Is that right? It's original page	10:50:32
14	108, stamped page 113.	10:50:47
15	A Okay, there we go. Yeah, got it.	10:50:50
16	Q Okay. And paragraph 235 starts with a	10:50:52
17	statement that your opinion that the combination	10:51:00
18	of Linnarsson and McCloskey, in view of knowledge	10:51:03
19	of a POSA, renders obvious claim 1, right?	10:51:07
20	A I believe it's claim 5.	10:51:13
21	Q In paragraph 235, you start with sort of	10:51:17
22	an introductory paragraph stating that Linnarsson	10:51:27

1	and McCloskey renders obvious the method of	10:51:29
2	claim 1.	10:51:33
3	Do you see that?	10:51:33
4	A Well, I -- I see that, but it says, quote:	10:51:34
5	Method of claim 1 wherein the tagged	10:51:37
6	polynucleotide, they're generated through at least	
7	one ligation reaction.	
8	So, that's the whole --	
9	(Indiscernible crosstalk.)	10:51:41
10	Q Sorry.	10:51:41
11	A Claim 5, yeah.	10:51:44
12	Q That's right. I think I was looking for	10:51:44
13	the wrong paragraph here. Okay. Sorry.	10:51:46
14	When I was referring to 237 confusedly	10:52:01
15	earlier, that was actually the paragraph I wanted	10:52:05
16	to focus on.	10:52:08
17	And that references a POSA would have been	10:52:08
18	motivated to adopt McCloskey's teaching and modify	10:52:13
19	Linnarsson's design so the tags include a first	10:52:16
20	region and a second region. And it references	10:52:21
21	section 12(1)(f)(ii); is that right?	10:52:25
22	A I see that, yes.	10:52:29

1	A I do.	10:53:47
2	Q And does your ground 2 theory rely on	10:53:47
3	hug's disclosure of a linker molecule to achieve	10:53:52
4	ligation?	10:53:58
5	A So, I didn't -- again, the -- the basis of	10:53:58
6	the opinion is Linnarsson in view of McCloskey and	10:54:02
7	knowledge available to a person of ordinary skill	10:54:08
8	in the art.	10:54:10
9	And Hug is certainly one example, but	10:54:11
10	there is a series of other citations that are --	10:54:14
11	essentially I use them that they are evidence that	10:54:18
12	ligation was a very commonly used technique to add	10:54:21
13	oligos to help track, you know, to add identifier	10:54:27
14	molecules to input libraries before sequencing and	10:54:31
15	for other purposes.	10:54:35
16	So, Hug was one specific example, but it	10:54:35
17	was part of a state -- a universe of many possible	10:54:38
18	examples of ligation being a very common technique	10:54:42
19	available to a person of skill in the art.	10:54:47
20	Q And Hug relies on linkers to achieve the	10:54:51
21	ligation; is that correct?	10:54:59
22	A So, yeah, Hug provides details for one	10:55:01

1 particular ligation protocol. It allows one to 10:55:05
2 get oligos to help differentiate different 10:55:08
3 templates. Again, it was mostly as a 10:55:13
4 demonstration of this is just one ligation method 10:55:14
5 that would have been available to a POSA, among a 10:55:17
6 set of others, which, again, would have been 10:55:20
7 common knowledge. 10:55:22

8 Q All right. And the linker and Hug is 10:55:23
9 designed to hybridize with the end of DNA cut by a 10:55:27
10 particular restriction enzyme; is that correct? 10:55:31

11 A So, that -- that's right. So, Hug -- Hug 10:55:31
12 had a strategy where you have a sort of sticky end 10:55:34
13 that was generated by a restriction enzyme, and 10:55:38
14 you take advantage of that to dangle a primer off 10:55:40
15 of it. And then that linker primer allows you to 10:55:43
16 add other primers to it and then ligate them 10:55:47
17 together. 10:55:49

18 Q And the Hug linkers, do they hybridize to 10:55:50
19 each other? 10:55:53

20 A Well, I think there was a couple schemes, 10:55:54
21 but one of -- yes, one of them involved 10:55:57
22 essentially a series of -- of oligos that provided 10:56:01

1 variable number of oligos that get added. So,
2 they -- they do self -- they are complementary to
3 themselves, and they can add anywhere between one
4 and a handful of different primers. And then that
5 was useful. In that particular implementation,
6 they were using that -- basically the number of
7 repeated primer units that got added was the way
8 that you could differentiate different input
9 molecules.

10 Q And does Linnarsson describe cutting the
11 ends of its cDNA with a restriction enzyme?

12 A Well, I -- yes, I believe there are -- I
13 believe figure 11 included an example of that. I
14 think there was a -- a BTS site, if I recall.
15 But, yes, I think that restriction cutting is
16 certainly one of the options contemplated by
17 Linnarsson.

18 Q Do you discuss that in ground 2 of your
19 declaration?

20 A Do I discuss the BTS site specifically in
21 figure 11 or --

22 Q Do you discuss Linnarsson's cutting cDNA

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1	with a restriction enzyme in ground 2 of your	10:57:31
2	report?	10:57:34
3	A I don't believe I explicitly highlighted	10:57:35
4	that, no.	10:57:38
5	Q Okay. Your ground 2 theory, I'm just sort	10:57:39
6	of trying to understand what the ultimate	10:57:55
7	combination is.	10:57:58
8	Are you -- is your theory that additional	10:57:59
9	tags would be ligated to the already existing tags	10:58:06
10	within the CDS or TSO from your ground 1	10:58:12
11	combination?	10:58:16
12	A So, I think it's -- it's that -- the one	10:58:21
13	example that we talked about is ligating --	10:58:23
14	ligating a molecular identifier or, you know, the	10:58:27
15	thing that allows you to solve the amplification	10:58:30
16	bias problem, that you could ligate that on to the	10:58:34
17	CDS or the TSO, or both, is what I wrote in my	10:58:36
18	report.	10:58:41
19	And that that would have been, you know, a	10:58:41
20	routine and conventional design choice available	10:58:43
21	to a person of ordinary skill in the art.	10:58:45
22	Q In ground 1 that you're building on for	10:58:51

1 ground 2, the CDS or TSO in ground 1 already has a 10:58:57
2 molecular identifier; is that correct, in your 10:59:02
3 opinion? 10:59:06

4 A So, yes, the -- I think the -- the one 10:59:07
5 step that required the second tag that is that 10:59:11
6 molecular identifier, that if you combine 10:59:15
7 Linnarsson with the teaching of McCloskey, that 10:59:20
8 you have multifunctional tags, essentially, that 10:59:22
9 you have tags that serve to track different levels 10:59:25
10 of the experiment, including individual templates. 10:59:29

11 So, yes, that's primarily that you could 10:59:31
12 modify the CDS/TSO, or both to make them function 10:59:34
13 similarly to the McCloskey version of the tag. 10:59:40

14 Q Okay. I apologize. I think I'm still a 10:59:47
15 little bit confused. 10:59:52

16 So, in ground 1, I think you have taken 10:59:52
17 the sequence in the CDS or TSO, you know, it 11:00:11
18 includes McCloskey, or some parts of McCloskey 11:00:12
19 that include a molecular identifier, right? 11:00:14

20 A That's -- that's correct. 11:00:19

21 Q Okay. 11:00:20

22 A Yeah, a -- when I say "molecular 11:00:21

1 identifier," meaning a tag that allows you to 11:00:25
2 track individual input templates, so that solves 11:00:27
3 that amplification bias problem. 11:00:33

4 Q Okay. And then in ground 2, you're 11:00:33
5 ligating a molecular identifier to the end of 11:00:36
6 something from the ground 1 combination? 11:00:44

7 A So, it is to the -- basically, that you 11:00:50
8 take the Linnarsson process through to the point 11:00:52
9 where you're putting the CDS and TSO on either 11:00:54
10 end, and then you can ligate after you've made the 11:00:58
11 initial cDNA, but before you then -- before the 11:01:01
12 subsequent PCR cycles that happen. 11:01:07

13 Q Okay. And where do you describe in your 11:01:09
14 report that that ligation happens after you made 11:01:12
15 the initial cDNA but before the PCR cycles that 11:01:18
16 happen? 11:01:23

17 A So, that is part of the -- again, that's 11:01:24
18 part of the McCloskey teaching. And -- and what's 11:01:28
19 generally known about solving the amplification 11:01:31
20 bias problem requires you to add the tag before 11:01:35
21 amplification. 11:01:38

22 Q In your ground 2 analysis, where do you 11:01:38

1	describe when the ligation happens?	11:01:43
2	A I'm sorry, are you there?	11:02:11
3	Q Sure. Yes.	11:02:13
4	A Sorry, my Zoom just crashed. So,	11:02:14
5	apparently my internet just had a problem. I'm	11:02:17
6	sorry, can we go back a minute and say where we	11:02:19
7	were?	11:02:22
8	Q Sure. I was asking where do you describe	11:02:22
9	in your ground 2 analysis when the ligation	11:02:24
10	happens?	11:02:28
11	A So, I think in paragraph 240, I said	11:02:30
12	ligating an additional sequence to Linnarsson CDS	11:02:34
13	and TSO.	11:02:37
14	And -- and so, I guess I did not	11:02:38
15	explicitly say a timing element there, but, again,	11:02:41
16	I -- I think it would be clear and obvious to a	11:02:48
17	person of skill in the art, understanding	11:02:51
18	McCloskey's teachings and -- and combining them	11:02:54
19	with Linnarsson, that that's what they would do.	11:02:57
20	It would be a natural -- a natural thing that they	11:03:00
21	would do.	11:03:01
22	Q Okay. And then going back to sort of the	11:03:02

1 question we were working on right before that, 11:03:05
2 when I was -- I was asking whether your ground 2 11:03:08
3 theory involves ligating a molecular identifier as 11:03:12
4 an additional tag on top of the already existing 11:03:21
5 tags within the CDS or TSO, including a molecular 11:03:25
6 identifier. And let me go back. 11:03:30

7 So, my understanding -- I'm sorry, this is 11:03:32
8 repeating myself a little bit -- from ground 1, is 11:03:35
9 that your opinion is that the CDS or TSO in ground 11:03:38
10 1 includes two tags, one of which is a molecular 11:03:42
11 identifier; is that right? 11:03:46

12 A It -- so, sorry, within ground 1, that the 11:03:49
13 CDS or TSO would be designed -- that the -- the 11:03:54
14 CDS and/or TSO would be designed to include both a 11:03:59
15 single cell tag or a batch -- you know, in the 11:04:04
16 parlance of McCloskey, a batch stamp, and a 11:04:06
17 molecular identifier, yes. 11:04:09

18 So, that would happen in the -- basically 11:04:11
19 in the extension/synthesis process of the initial 11:04:13
20 cDNA synthesis. 11:04:19

21 Q Then in ground 2, you build on ground 1, 11:04:20
22 right? 11:04:24

1	A Well, yes, except you would...	11:04:24
2	(Technical difficulty.)	11:04:45
3	(Off the record.)	11:04:45
4	BY MS. RAYMOND:	11:05:10
5	Q Dr. Cooper, right before we had	11:05:16
6	internet-connection difficulties, I had asked a	11:05:19
7	question, which was: Then in ground 2, you build	11:05:22
8	on ground 1, right?	11:05:25
9	And you started, and you said: Well, yes,	11:05:26
10	you would -- and then we got caught off.	11:05:28
11	Can you continue your answer, please?	11:05:32
12	A Okay. Yes, the -- the general idea is	11:05:34
13	that you -- it's a different -- it's a different	11:05:35
14	specific formulation to -- to essentially generate	11:05:38
15	a McCloskey style tag where you have multiple	11:05:43
16	elements. But one portion of it would be the --	11:05:46
17	you know, the CDS or TSO would be the -- the cell	11:05:49
18	tag, and then you would ligate on the UMI, which	11:05:52
19	creates a McCloskey style tag that has multiple	11:05:55
20	functional domains in it.	11:05:58
21	Basically, the end of that process, you	11:06:00
22	end up with an individual cDNAs that have both the	11:06:02

1	cell and a molecular tag on them.	11:06:06
2	Q So, you said it's a different specific	11:06:10
3	formulation; is that right? Do I have the	11:06:18
4	language right?	11:06:22
5	(Indiscernible crosstalk.)	11:06:22
6	A One version would involve ligation, and	11:06:22
7	the other wouldn't. And, again, that's just sort	11:06:24
8	of a -- a design choice that you could optimize to	11:06:26
9	your particular needs and goals, and it would just	11:06:31
10	be a matter of flexibility for different kinds	11:06:34
11	of -- different kinds of setups that allow you	11:06:38
12	maximize efficiency of your overall process.	11:06:41
13	Q And I apologize, I think I'm still not	11:06:45
14	quite understanding whether your ground 2 opinion	11:07:02
15	builds and modifies from your ground 1 opinion or	11:07:10
16	whether it starts over with Linnarsson.	11:07:13
17	A Okay.	11:07:18
18	MR. WALTER: Objection, form.	11:07:18
19	A So, it certainly doesn't start over,	11:07:21
20	right? So, we have -- so, claim 5 depends on	11:07:24
21	claim 1, and so we have all the elements of	11:07:27
22	providing a sample and doing single cells, and so	11:07:30

1 all of that is carried forward the same. 11:07:33

2 It's just the -- the particular step of 11:07:35

3 how one adds the molecular identifier or the 11:07:39

4 second tag in the -- the verbiage of the claim. 11:07:43

5 So, that's -- that's the difference that one would 11:07:47

6 make is, instead of include -- embedding that 11:07:48

7 within the CDS and TSO, you would ligate it on 11:07:52

8 after the that initial cDNA had been made. 11:07:56

9 Q Okay. And where in your report do you 11:07:58

10 describe that the ligation happens instead 11:08:02

11 embedding the molecular identifier into the CDS or 11:08:07

12 TSO? 11:08:14

13 A Well, I think I talk about it in 11:08:17

14 paragraph -- yeah, paragraph 237, where it says 11:08:19

15 specifically that you ligate an oligonucleotide 11:08:28

16 comprising a second tag sequence to Linnarsson's 11:08:31

17 CDS and/or TSO. 11:08:33

18 (The court reporter asked for clarification.) 11:08:33

19 A But -- so, paragraph 237 that ends with: 11:08:37

20 Ligating an oligonucleotide comprising a second 11:08:42

21 tag sequence to Linnarsson's CDS and/or TSO. 11:08:48

22 Q And do you say there that you would not 11:08:57

1	include the second tag sequence within	11:09:02
2	Linnarsson's CDS and/or TSO as you did in	11:09:13
3	ground 1? Do you explain that in your report?	11:09:17
4	A I guess, to me, that -- that was an	11:09:20
5	obvious inference from that is that you're using	11:09:22
6	the basic design of the Linnarsson CDS or TSO and	11:09:25
7	then ligating on the additional piece to	11:09:29
8	eventually form what is, you know, a	11:09:33
9	multifunctional tag sequence at either end of the	11:09:36
10	cDNA, or both.	11:09:39
11	Q Have you read the institution decision in	11:09:41
12	this case?	11:09:50
13	Do you know what that is?	11:09:50
14	A I -- I do, and I -- I wouldn't say I read	11:09:53
15	every word, but I have certainly looked at it.	11:09:56
16	Q Do you recall disagreeing with anything in	11:09:59
17	the institution decision?	11:10:01
18	A Oh, I -- nothing that I'd be willing to	11:10:03
19	formally say -- you know, I didn't -- I --	11:10:06
20	certainly, it's not part of my report. And I --	11:10:07
21	I -- I read it and I had a general understanding	11:10:10
22	of, but I can't recall any details of reactions	11:10:12

1	one way or another.	11:10:15
2	Q Do you recall that the board said for	11:10:19
3	ground 1 a POSITA could conceptually divide each	11:10:25
4	of Linnarsson's cell tag sequences into two	11:10:29
5	portions, where the first portion performs the	11:10:32
6	function of McCloskey's batch stamp and the second	11:10:35
7	performs the function of McCloskey's barcode?	11:10:38
8	Do you recall that?	11:10:41
9	A That sounds correct.	11:10:42
10	Q Okay. And did you agree with the board as	11:10:43
11	to that being consistent with your theory of what	11:10:48
12	the combination is in ground 1?	11:10:51
13	A I mean, without going to a full detailed	11:10:55
14	analysis, yes, that sounds generally correct, yes.	11:10:58
15	MS. RAYMOND: If we could go off the	11:11:04
16	record for maybe five minutes, we may be able to	11:11:07
17	finish up pretty quickly.	11:11:12
18	(Off the record.)	11:11:14
19	MS. RAYMOND: Dr. Cooper, thank you so	11:18:29
20	much for your time today. I don't have any	11:18:31
21	further questions.	11:18:33
22	MR. WALTER: Dr. Cooper, I have a few	11:18:34

1	questions.	11:18:36
2	EXAMINATION	11:18:37
3	BY MR. WALTER:	11:18:37
4	Q Do you recall on cross-examination you	11:18:39
5	were asked some questions about the timing of	11:18:41
6	introducing a molecular tag to the CDS or TSO?	11:18:43
7	A Yes.	11:18:48
8	Q What, if anything, to your knowledge, of	11:18:48
9	the claims state with regard to the timing of	11:18:53
10	introducing a molecular tag by ligation?	11:18:57
11	A So, I -- I don't -- the -- the claim	11:19:01
12	itself just says that the tag to polynucleotides	11:19:03
13	are generated through at least one ligation	11:19:07
14	reaction, so the claim is general with respect to	11:19:11
15	timing.	11:19:13
16	Q Okay. Now, one of the things you said is	11:19:14
17	it would be natural to do it before a PCR	11:19:15
18	amplification process.	11:19:20
19	Do you recall that?	11:19:21
20	A I do.	11:19:21
21	Q Why is that?	11:19:22
22	A Because the -- again, because reading	11:19:26

1 McCloskey, the -- the benefit of that molecular 11:19:28
2 identifier tag is to reduce or eliminate skewed 11:19:31
3 amplification. And so, the -- the earlier you do 11:19:38
4 it in terms of before amplification, that's more 11:19:39
5 effective at solving that problem. 11:19:42

6 Q Okay. Where do you explain that in your 11:19:43
7 report? 11:19:47

8 A There is a -- an entire section on 11:19:47
9 amplification bias early in the report. I don't 11:19:50
10 remember the exact paragraph numbers, but there 11:19:52
11 is -- 11:19:54

12 Q Can you take a look and please identify 11:19:55
13 those paragraph numbers? 11:20:03

14 A Sure. So, it starts at paragraph 90. 11:20:04
15 That's one area. And I believe there are other 11:20:13
16 areas, as well. So, paragraph -- so, in general, 11:20:16
17 we talk about paragraph -- we talk about 11:20:25
18 McCloskey, specifically starting at paragraph 99 11:20:25
19 through 10 -- at least 104, yeah, so those -- 11:20:29
20 those sections at least. 11:20:39

21 MR. WALTER: All right. No questions from 11:20:41
22 me. 11:20:43

1 MS. RAYMOND: No follow-up here.

11:20:44

2 (Proceeding concluded at 11:20 a.m.)

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Transcript of Gregory Cooper, Ph.D.
Conducted on December 20, 2023

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CERTIFICATE OF SHORTHAND REPORTER - NOTARY PUBLIC

I, Karen Klerekoper, Certified Reporter and Notary Public within and for the State of Michigan do hereby certify: That GREGORY COOPER, PhD, the witness whose deposition is hereinbefore set forth, was duly sworn by me before the commencement of such deposition and that such deposition was taken before me and is a true record of the testimony given by such witness.

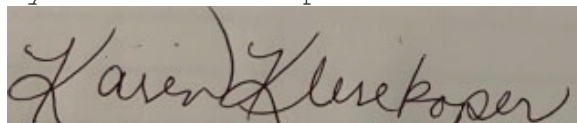
I further certify that the adverse party, 10X GENOMICS, INC., was represented by counsel at the deposition.

I further certify that the deposition of GREGORY COOPER, PhD, occurred remotely via Zoom on WEDNESDAY, DECEMBER 20, 2023, from 9:56 a.m. Eastern Standard Time to 11:20 a.m. Eastern Standard Time.

I further certify that I am not related to any of the parties to this action by blood or marriage, I am not employed by or an attorney to any of the parties to this action, and that I am in no way interested, financially or otherwise, in the transcript of GREGORY COOPER, PhD, conducted on December 20, 2023, in the outcome of this matter.

IN THE WITNESS WHEREOF, I have hereunto set my hand this 21st day of December, 2023.

My commission expires: October 7, 2024.



KAREN KLEREKOPER, NOTARY PUBLIC IN AND FOR THE
STATE OF MICHIGAN, OAKLAND COUNTY