

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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Exhibit 1002,

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Exhibit 1003, Linnarsson

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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

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 Q Okay. And so I'm just trying to 10:52:30
2 understand sort of your starting point for 10:52:33
3 ground 2 and whether your starting point for 10:52:38
4 ground 2 is your ground 1 combination that you 10:52:41
5 further modify? 10:52:44

6 A Yes, I -- yes, I believe that's right, 10:52:46
7 because I think the -- the McCloskey/Linnarsson 10:52:48
8 combination for obviousness was relevant to the 10:52:54
9 obviousness of claim 1, so it carries forward 10:52:58
10 through to the dependent claim, yes. 10:53:01

11 Q So you start with your ground 1 10:53:03
12 combination, and then you further modify it to 10:53:04
13 address the limitation of the tagged 10:53:08
14 polynucleotides that are generated through at 10:53:11
15 least one ligation reaction? 10:53:13

16 A That's right, with -- with the additional 10:53:15
17 component being the knowledge of a person of 10:53:19
18 ordinary skill in the art. 10:53:22

19 Q And you have later in this section, for 10:53:24
20 example, in paragraphs 240 through 242, at least, 10:53:36
21 a discussion of the Hug reference. Do you see 10:53:42
22 that? 10:53:46

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.)

11:20:48

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1 CERTIFICATE OF SHORTHAND REPORTER - NOTARY PUBLIC

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

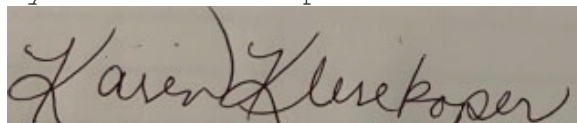
10 I further certify that the adverse
11 party, 10X GENOMICS, INC., was represented by
12 counsel at the deposition.

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

18 I further certify that I am not related
19 to any of the parties to this action by blood or
20 marriage, I am not employed by or an attorney to
21 any of the parties to this action, and that I am
22 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