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 _____

14 DEPOSITION OF GREGORY COOPER, PhD

15 Wednesday, December 20, 2023

16 9:56 a.m. EST

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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10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00002

1 A P P E A R A N C E S
2
3 ON BEHALF OF THE PETITIONER, PARSE
4 BIOSCIENCES, INC.:
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12 ON BEHALF OF THE PATENT OWNER, 10X
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22

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00003

INDEX

WITNESS: PAGE:

GREGORY COOPER, PhD

EXAMINATION BY MS. RAYMOND: 5

EXAMINATION BY MR. WALTER: 61

*****

EXHIBIT: PAGE:

Exhibit 1002, 6

Exhibit 1003, Linnarsson 21

Exhibit 1004, McCloskey 32

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10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00004

1 P R O C E E D I N G S
2 (Oath stipulation read and agreed by counsel 09:54:41
3 and witness.) 09:54:41
4 GREGORY COOPER, PhD, having been duly sworn 09:55:05
5 testified as follows: 09:56:14
6 EXAMINATION 09:56:14
7 BY MS. RAYMOND: 09:56:15
8 Q Dr. Cooper, could you just state your name 09:56:15
9 for the record, please. 09:56:21
10 A Sure. My name is Greg Cooper. 09:56:22
11 Q Thank you. Thanks for joining us this 09:56:25
12 morning. 09:56:28
13 And are you the person that wrote an 09:56:29
14 expert report in IPR2023-00876? 09:56:31
15 A Yes. 09:56:36
16 Q Okay. 09:56:38
17 MS. RAYMOND: And I don't know if the tech 09:56:39
18 is able to bring up Exhibit 1002 on to the screen. 09:56:42
19 Great, thank you. 09:56:56
20 Q And, Dr. Cooper, the report that's being 09:56:57
21 shown here that has a stamp, if we can scroll down 09:56:59
22 on the bottom right is Exhibit 1002. Do you see 09:57:03

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00005

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00006

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 chromatins, 09:59:13
22 so experiments that measure how open or closed a 09:59:17

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00007

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00008

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00009

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00010

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00011

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00012

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00013

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00014

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00015

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00016

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00017

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00018

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00019

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00020

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00021

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00022

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00023

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00024

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00025

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00026

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00027

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00028

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00029

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00030

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00031

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00032

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00033

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00034

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00035

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00036

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00037

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00038

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00039

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00040

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00041

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00042

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00043

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00044

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00045

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00046

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00047

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00048

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00049

1 variable number of oligos that get added. So, 10:56:06
2 they -- they do self -- they are complementary to 10:56:10
3 themselves, and they can add anywhere between one 10:56:13
4 and a handful of different primers. And then that 10:56:15
5 was useful. In that particular implementation, 10:56:19
6 they were using that -- basically the number of 10:56:22
7 repeated primer units that got added was the way 10:56:25
8 that you could differentiate different input 10:56:28
9 molecules. 10:56:31
10 Q And does Linnarsson describe cutting the 10:56:31
11 ends of its cDNA with a restriction enzyme? 10:56:42
12 A Well, I -- yes, I believe there are -- I 10:56:48
13 believe figure 11 included an example of that. I 10:56:52
14 think there was a -- a BTS site, if I recall. 10:56:55
15 But, yes, I think that restriction cutting is 10:56:58
16 certainly one of the options contemplated by 10:57:02
17 Linnarsson. 10:57:04
18 Q Do you discuss that in ground 2 of your 10:57:05
19 declaration? 10:57:19
20 A Do I discuss the BTS site specifically in 10:57:22
21 figure 11 or -- 10:57:27
22 Q Do you discuss Linnarsson's cutting cDNA 10:57:27

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00050

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00051

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00052

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00053

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00054

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00055

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00056

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00057

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00058

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00059

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00060

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00061

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00062

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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10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955

1 CERTIFICATE OF SHORTHAND REPORTER - NOTARY PUBLIC

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

I further certify that the adverse
7 party, 10X GENOMICS, INC., was represented by
counsel at the deposition.
8

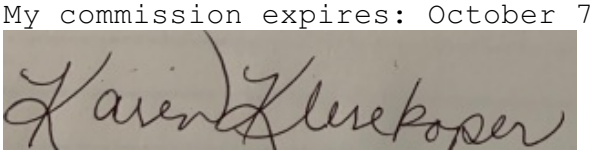
I further certify that the deposition of
9 GREGORY COOPER, PhD, occurred remotely via Zoom on
WEDNESDAY, DECEMBER 20, 2023, from 9:56 a.m.
10 Eastern Standard Time to 11:20 a.m. Eastern
Standard Time.
11

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

16

17 IN THE WITNESS WHEREOF, I have hereunto set my
hand this 21st day of December, 2023.
18

My commission expires: October 7, 2024.
19



20

_____
21

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

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00064

A
ability 10:14
able 5:18, 12:4, 17:8, 60:16
about 10:1, 11:15, 12:5, 12:6, 14:11, 14:18, 14:20, 16:12, 18:8, 19:3, 23:17, 25:1, 25:2, 25:3, 25:9, 27:14, 30:5, 32:2, 34:11, 36:2, 36:8, 37:1, 38:2, 38:3, 38:8, 39:3, 39:9, 42:11, 51:13, 53:19, 58:13, 61:5, 62:17
absolutely 30:17
abstract 36:19
access 6:6, 17:5
achieve 48:3, 48:20
acronym 22:18
across 10:17, 35:12, 35:16, 42:3
action 64:22, 64:24
active 8:13, 9:16
actual 20:9
actually 6:16, 32:11, 34:11, 41:19, 46:15
adapters 32:12
add 20:15, 20:18, 48:12, 48:13, 49:16, 50:3, 53:20
added 18:12, 26:19, 35:5, 50:1, 50:7
adding 18:19, 20:13, 24:12, 33:19
addition 28:5, 28:15
additional 12:3, 47:16, 51:8, 54:12, 55:4, 59:7
address 47:13
addressed 39:2
addressing 37:9
adds 26:5, 58:3
adopt 46:18
advantage 26:7, 31:18, 36:3, 49:14
adverse 64:11
affect 19:5
after 20:13, 20:20, 20:21, 33:22, 36:5, 53:10, 53:14, 58:8
again 9:14, 12:3, 13:10, 14:5, 14:13, 23:9, 28:6, 28:8, 29:18, 29:22, 30:7, 31:4, 34:7, 36:7, 43:9, 43:15, 44:15, 48:5, 49:3, 49:6, 53:17, 54:15, 57:7, 61:22
agree 30:13, 60:10
agreed 5:2
ahead 34:5
all 10:13, 10:17, 11:1, 11:3, 19:9, 20:10, 23:11, 23:19, 28:7, 40:19, 49:8, 57:21, 58:1, 62:21
alleles 35:21
allow 32:13, 57:11
allows 8:20, 20:3, 24:8, 29:3, 41:7, 49:1, 49:15, 51:15, 53:1
already 51:9, 52:1, 55:4
also 3:20, 12:11, 38:3
although 36:7
always 30:22
among 49:5
amplification 18:9, 18:13, 18:17, 18:21, 19:1, 19:4, 19:12, 19:22, 20:13, 20:14, 20:15, 37:2, 37:12, 37:18, 40:18, 41:1, 41:7, 41:9, 51:15, 53:3, 53:19, 53:21, 61:18, 62:3, 62:4, 62:9
amplified 19:8, 29:12
amplify 29:1, 29:4
amplifying 19:14
analyses 12:17
analysis 8:10, 8:11, 8:20, 9:20, 10:2, 10:5, 10:6, 10:7, 10:8, 10:11, 11:9, 11:11, 13:12, 13:15, 15:6, 53:22, 54:9, 60:14
analyzing 40:11
anneal 26:11, 33:19, 35:21
annealed 34:14
another 19:15, 19:18, 31:4, 44:15, 45:8, 60:1
answer 56:11
any 8:14, 9:9, 9:12, 10:14, 10:16, 20:1, 29:20, 30:9, 31:10, 32:4, 37:8, 43:21, 45:2, 59:22, 60:20, 64:22,

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00065

64:24
anything
16:14, 40:3, 44:17, 59:16, 61:8
anywhere
44:9, 44:10, 50:3
apologize
52:14, 57:13
apparently
54:5
appeal
1:3
applies
37:19
apply
16:6
area
62:15
areas
62:16
art
47:18, 48:8, 48:19, 51:21, 54:17
asked
10:1, 10:7, 56:6, 58:18, 61:5
asking
54:8, 55:2
aspect
11:10
assign
10:15
assigned
12:19, 13:13, 13:19
assigning
10:19
assume
32:22
attach
29:2
attorney
64:23
available
15:21, 48:7, 48:19, 49:5, 51:20
average
10:17
aware
43:21

B

back
12:3, 16:5, 28:8, 32:15, 37:20, 54:6, 54:22, 55:6
backing
18:7
bar
36:21
barcode
27:3, 60:7
base
42:20
basic
59:6
basically
31:15, 50:6, 53:7, 55:18, 56:21
basis
8:21, 9:17, 10:20, 11:2, 11:6, 14:16, 40:13, 48:5
batch
35:8, 35:11, 35:16, 36:20, 38:9, 55:15, 55:16, 60:6
baughman
3:7
bead
44:7, 44:19
beads
31:19, 44:14
because
14:5, 19:11, 23:13, 39:11, 47:7, 61:22
been
5:4, 15:4, 15:6, 17:1, 46:17, 49:5, 49:6, 51:19, 58:8
before
1:3, 2:7, 20:4, 20:15, 20:22, 34:15, 48:14, 53:11, 53:15, 53:20, 55:1, 56:5, 61:17, 62:4, 64:6, 64:8
beginning
18:10, 28:21
behalf
3:3, 3:12
behavior
7:11
being
5:20, 19:9, 26:17, 30:8, 39:14, 47:17, 48:18, 60:11
believe
24:17, 25:14, 27:6, 37:11, 38:9, 39:11, 40:4, 45:13, 45:20, 47:6, 50:12, 50:13, 51:3, 62:15
bell
22:17
benefit
62:1
better
11:21, 20:21
between
36:3, 42:19, 50:3
bias
18:9, 18:17, 18:22, 19:2, 19:22, 20:14, 37:3, 37:12, 37:19, 40:18, 41:1, 41:9, 51:16, 53:3, 53:20, 62:9
bio
25:11
biology
7:6
biosciences
1:5, 3:4
biotin
25:15, 25:21, 31:20
bit
7:15, 11:20, 16:10, 21:3, 21:4, 22:20, 26:20, 52:15, 55:8
block
41:14, 41:19
blood
64:22
board
1:3, 60:2, 60:10
boss
7:5
both
51:17, 52:12, 55:14, 56:22, 59:10
bottom
5:22, 8:5, 24:15, 25:11
brad
3:21
brady
15:8, 16:2, 16:19, 17:9
brail
15:9, 16:2, 16:19, 17:9
break
45:2, 45:3
breaks
45:6
bring
5:18, 45:11
broad
9:4, 9:10

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00066

bts
27:18, 27:21, 50:14, 50:20
buffer
34:3
build
55:21, 56:7
building
51:22
builds
57:15
bulk
8:10, 8:11, 9:19, 10:2, 10:5, 10:6, 10:7, 10:8, 10:11
bunch
10:11, 11:9, 20:5

C

california
3:17
call
16:9, 23:12, 26:9, 29:11
called
25:14, 26:10
can't
19:22, 22:17, 36:17, 42:22, 59:22
carried
58:1
carries
27:11, 47:9
carry
27:3
case
14:20, 25:19, 33:10, 34:11, 36:6, 59:12
cases
17:17
caught
56:10
caused
8:12
cd
29:1
cdna
26:15, 26:17, 27:3, 29:2, 42:5, 42:6, 43:12, 50:11, 50:22, 53:11, 53:15, 55:20, 58:8, 59:10
cdnas
56:22
cds
22:6, 24:16, 24:19, 24:21, 25:2, 25:7, 25:18, 51:10, 51:17, 52:1, 52:12, 52:17, 53:9, 54:12, 55:5, 55:9, 55:13, 55:14, 56:17, 58:7, 58:11, 58:17, 58:21, 59:2, 59:6, 61:6
cell
8:14, 9:20, 10:3, 10:6, 10:7, 10:16, 10:18, 10:19, 10:22, 11:5, 11:18, 12:2, 12:5, 12:6, 12:18, 13:1, 13:3, 13:8, 13:19, 13:20, 14:18, 14:22, 15:2, 16:21, 17:10, 35:2, 38:12, 39:4, 55:15, 56:17, 57:1, 60:4
cell-by-cell
9:16, 11:1, 11:6, 14:16, 40:13
cells
8:12, 9:5, 9:8, 9:11, 9:13, 10:11, 10:14, 10:17, 11:1, 11:3, 11:10, 11:12, 11:19, 11:22, 12:11, 12:19, 13:14, 15:6, 16:8, 16:18, 16:21, 17:11, 17:17, 22:7, 34:19, 40:12, 57:22
certain
19:5
certainly
15:21, 21:5, 22:8, 22:11, 23:11, 24:22, 25:4, 30:10, 32:5, 39:12, 40:1, 40:4, 42:17, 43:17, 48:9, 50:16, 57:19, 59:15, 59:20
certificate
64:1
certified
64:2
certify
64:4, 64:11, 64:15, 64:21
choice
51:20, 57:8
chromatin
7:13
chromatins
7:21
citation
41:14
citations
48:10
cite
38:13, 41:22, 42:15, 44:3
cited
21:12, 29:18, 39:19
cites
39:4
citing
21:18, 44:17
claim
29:20, 32:4, 45:19, 45:20, 46:2, 46:5, 46:11, 47:9, 47:10, 57:20, 57:21, 58:4, 61:11, 61:14
claims
28:4, 30:9, 61:9
clarification
58:18
clean
25:17, 27:20, 31:16, 31:20
clear
54:16
clearly
36:10, 36:14, 37:5
cleaved
33:5, 34:1
close
7:4
closed
7:22
codes
36:21
collaborated
7:8
collaborators
7:4
colleague
7:5
com
14:14
combination
40:3, 45:17, 47:4, 47:8, 47:12, 51:7, 51:11, 53:6, 60:12
combine
52:6

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00067

combined
12:3
combining
54:18
come
9:18
comes
12:22
comfortable
16:7, 16:16, 17:14, 17:19
coming
23:16
commencement
64:7
commission
64:33
common
19:4, 48:18, 49:7
commonly
48:12
complement
24:13
complementarity
36:3
complementary
24:8, 50:2
complete
26:14
component
47:17
comprising
58:16, 58:20
concentration
19:19
concept
43:10, 43:18
conceptual
10:21, 16:11
conceptually
60:3
concluded
63:2
conclusions
29:16
conducted
2:2, 64:26
confused
52:15
confusedly
46:14
connected
31:20
consequence
27:2
consistent
35:12, 42:12, 60:11
contamination
38:2
contemplated
50:16
content
32:13
continue
56:11
continues
37:13
control
19:22
convenient
45:6
conventional
51:20
cooper
1:15, 2:2, 4:5, 5:4, 5:8, 5:10, 5:20, 6:19, 22:3, 32:22, 45:2, 56:5, 60:19, 60:22, 64:4, 64:16, 64:26
cooper's
6:4
copies
19:18, 20:5, 20:11, 29:12
copy
27:11
correct
6:8, 11:2, 13:15, 13:16, 18:17, 18:18, 20:16, 23:17, 23:18, 24:16, 24:19, 24:21, 25:8, 28:4, 28:18, 29:6, 35:9, 44:20, 48:21, 49:10, 52:2, 52:20, 60:9, 60:14
could
5:8, 6:11, 7:2, 8:3, 9:7, 9:8, 9:11, 9:17, 11:16, 15:3, 18:1, 20:19, 21:2, 21:21, 29:8, 31:12, 32:7, 32:15, 32:16, 37:20, 41:10, 42:19, 50:8, 51:16, 52:11, 57:8, 60:3, 60:15
couldn't
34:22
counsel
5:2, 64:13
count
20:6
county
64:39
couple
34:15, 49:20
course
15:18
court
58:18
crashed
54:4
creates
56:19
crisply
26:21
cross-examination
61:4
crosstalk
34:4, 46:9, 57:5
cs
26:5, 26:8, 26:12
csr
1:26
cut
31:19, 49:9
cutting
29:10, 29:12, 50:10, 50:15, 50:22
cycles
21:1, 53:12, 53:15
cytosines
26:6

D

dangle
49:14
data
11:16, 12:20, 12:21, 12:22, 39:17
date
36:20
day
64:31
dc
3:9
debates
16:12
december
1:17, 64:17, 64:27, 64:31
decision
59:11, 59:17
declaration
6:4, 6:13, 8:4, 50:19
demonstration
49:4
depend
14:4
dependent
47:10
depends
13:7, 14:2, 57:20
depos
3:21

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00068

deposition
1:15, 2:2, 6:6, 64:5, 64:7, 64:8, 64:13, 64:15
derek
3:14
derived
20:10
describe
16:3, 16:20, 17:9, 26:1, 28:9, 31:5, 32:7, 40:11, 50:10, 53:13, 54:1, 54:8, 58:10
described
15:15, 15:17, 23:16
describes
26:22
describing
23:13, 43:22
description
33:12, 33:14
design
36:9, 37:7, 46:19, 51:20, 57:8, 59:6
designed
35:11, 35:21, 36:4, 49:9, 55:13, 55:14
detailed
60:13
details
16:22, 22:18, 35:13, 40:15, 40:19, 48:22, 59:22
detect
20:11, 36:21
difference
10:21, 58:5
differences
15:19, 15:22, 19:14, 19:16
different
6:8, 15:16, 19:11, 43:7, 49:2, 50:4, 50:8, 52:9, 56:13, 57:2, 57:10, 57:11
differentially
19:6
differentiate
49:2, 50:8
differs
9:20, 10:3
difficulties
56:6
difficulty
56:2
digest
34:9
digested
33:16, 34:2, 34:18, 35:6
digesting
33:11
disagreeing
59:16
disclose
33:8
disclosed
29:20, 35:14
discloses
28:7
disclosing
31:6, 43:17
disclosure
21:11, 22:10, 23:20, 30:10, 32:6, 43:21, 44:16, 48:3
disclosures
28:11
discuss
31:1, 36:12, 36:13, 50:18, 50:20, 50:22
discusses
37:18
discussing
31:3, 39:14
discussion
47:21
diseases
7:7
dish
9:5
diversity
37:3
divide
60:3
dna
7:12, 24:13, 27:8, 27:9, 27:10, 33:4, 33:9, 34:1, 34:2, 34:14, 34:18, 34:21, 35:6, 35:7, 36:6, 38:10, 49:9
dnase
31:9
document
6:7
doing
11:8, 13:7, 13:14, 14:7, 14:8, 14:10, 17:15, 44:22, 57:22
domains
56:20
dominant
19:3, 42:18
done
11:12
donor
9:6
double-stranded
26:15, 27:10
down
5:21, 6:16, 17:16, 33:3, 35:6
downstream
25:15
dr
5:8, 5:20, 6:4, 6:19, 22:3, 32:22, 45:2, 56:5, 60:19, 60:22
duly
5:4, 64:6
duplex
27:9

E

each
10:19, 11:5, 12:2, 13:4, 16:21, 17:10, 20:4, 20:7, 49:19, 60:3
earlier
20:17, 42:12, 46:15, 62:3
early
62:9
easier
10:8
eastern
64:18
eberwine
15:9, 16:3, 16:20, 17:9
edge
14:20
effective
20:18, 62:5
efficiency
19:14, 20:1, 57:12
either
16:3, 53:9, 59:9
element
12:8, 30:9, 32:4, 54:15
elements
7:12, 7:13, 9:16, 10:15, 22:8, 23:10, 29:21, 31:7, 56:16, 57:21
eliminate
62:2

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00069

else
19:9, 44:9, 44:10
embedding
58:6, 58:11
embodiment
28:10, 30:1, 43:6, 43:7
employed
64:23
encoding
34:13, 35:4, 35:7, 35:20
encompass
9:5, 9:7
encompasses
7:19
end
6:16, 6:19, 8:7, 18:7, 20:5, 20:9, 20:11, 24:5, 26:4, 26:11, 27:2, 29:3, 32:10, 37:14, 42:7, 44:1, 49:9, 49:12, 53:5, 53:10, 56:21, 56:22, 59:9
ended
34:10
ends
50:11, 58:19
entire
62:8
enzyme
24:12, 26:3, 49:10, 49:13, 50:11, 51:1
equal
19:9
especially
7:7, 7:9
esquire
3:5, 3:6, 3:14
essentially
7:20, 9:9, 9:12, 10:13, 25:16, 31:21, 32:9, 41:8, 48:11, 49:22, 52:8, 56:14
est
1:19
even
16:9, 19:13, 19:18
eventually
33:18, 59:8
ever
29:19, 31:8
every
59:15
everything
27:14
evidence
23:19, 25:5, 48:11
exact
35:14, 62:10
exactly
14:22, 40:5, 43:16
examination
4:6, 4:7, 5:6, 61:2
example
11:21, 12:9, 19:7, 21:12, 25:6, 25:8, 25:20, 28:6, 29:7, 30:1, 36:18, 39:13, 40:7, 47:20, 48:9, 48:16, 50:13, 51:13
examples
25:3, 48:18
except
56:1
exhibit
4:10, 4:13, 4:14, 4:15, 5:18, 5:22, 6:3, 21:6, 21:7, 21:22, 32:17, 32:18, 40:8
exhibits
6:5, 40:4
existing
51:9, 55:4
experience
6:20, 7:16
experiment
13:2, 13:3, 13:20, 14:2, 14:12, 20:12, 20:22, 34:8, 35:12, 35:17, 35:19, 52:10
experimental
33:12
experiments
7:20, 7:22, 12:10, 13:5
expert
5:14
expires
64:33
explain
9:19, 11:20, 59:3, 62:6
explicitly
51:3, 54:15
exponential
19:11, 19:13
expressed
8:14, 9:15
expression
7:12, 7:13, 7:21, 10:15, 15:5, 16:8, 16:18, 17:16, 17:21
extension
26:14, 55:19
extensive
6:20
extent
20:8, 32:4, 36:8

F

f1
33:5
fair
23:12
familiar
22:15
far
25:10
few
26:5, 33:3, 60:22
figure
21:11, 21:18, 22:1, 22:2, 22:3, 23:4, 23:7, 23:10, 23:19, 23:22, 24:1, 24:2, 24:18, 25:2, 25:10, 26:1, 26:16, 27:15, 27:18, 27:22, 28:2, 28:12, 28:17, 28:20, 29:8, 29:9, 29:18, 31:4, 31:12, 31:13, 32:5, 32:8, 32:9, 42:11, 42:13, 42:15, 43:7, 43:16, 44:8, 44:9, 44:13, 50:13, 50:21
figures
25:1, 28:15
financially
64:25
find
22:19
finish
60:17
first
22:15, 39:1, 46:19, 60:5
fit
33:1
five
24:4, 26:4, 42:7, 60:16

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00070

flexibility
57:10
focus
46:16
focused
40:17, 40:22
follow-up
63:1
follows
5:5
forgot
26:3
form
11:13, 12:14, 13:6, 14:1, 17:12, 19:4, 21:17, 23:6, 27:16, 28:14, 34:6, 40:14, 42:14, 43:8, 57:18, 59:8
formally
59:19
formed
26:18
forming
28:2, 29:5, 30:4, 32:1, 39:19
forms
42:18
formulation
56:14, 57:3
forth
64:6
forward
34:12, 47:9, 58:1
fragment
42:7, 43:1, 43:22, 44:6, 44:19
fragmentation
29:11, 29:19, 30:3, 30:6, 31:9
fragmented
30:21
fragmenting
42:6
fragments
42:20, 43:11, 43:18, 44:14
friend
7:5
front
22:2
full
39:1, 60:13
fun
16:12
function
37:3, 37:4, 52:12, 60:6, 60:7
functional
56:20
functions
8:14, 10:20
fundamentally
12:22, 14:13, 14:19, 19:21
further
47:5, 47:12, 60:21, 64:11, 64:15, 64:21

G

gather
12:20, 14:15
gathering
14:18
gene
7:11, 7:13, 7:21, 8:2, 15:5, 16:7, 16:17, 17:15, 17:21, 35:22
general
10:10, 12:17, 20:17, 35:11, 35:16, 36:1, 36:18, 37:1, 37:19, 42:16, 43:10, 56:12, 59:21, 61:14, 62:16
generalizable
36:10, 36:14, 37:6
generally
10:9, 34:9, 40:16, 40:21, 53:19, 60:14
generate
42:19, 56:14
generated
46:6, 47:14, 49:13, 61:13
genes
8:13, 9:15
genetic
34:20
genetics
16:13, 16:15
genomic
11:9, 12:18, 13:13, 13:18, 14:9, 14:15, 33:4, 34:1, 34:18, 36:6
genomics
1:8, 3:13, 8:19, 11:8, 11:11, 12:12, 13:5, 13:9, 13:21, 14:6, 14:10, 14:15, 14:17, 16:3, 16:9, 16:10, 16:12, 16:15, 64:12
getting
10:16, 10:22, 11:3, 11:4
given
8:15, 20:1, 64:9
go
8:11, 16:5, 28:8, 31:12, 32:15, 34:5, 36:5, 37:20, 38:18, 45:15, 54:6, 55:6, 60:15
goals
57:9
goes
8:8, 33:18, 39:3, 41:12
going
6:15, 6:16, 16:13, 21:14, 22:19, 27:20, 54:22, 60:13
gotshal
3:15
graphical
23:8
great
5:19, 6:10, 6:18, 22:13
greg
5:10
gregory
1:15, 2:2, 4:5, 5:4, 64:4, 64:16, 64:26
groombridge
3:7
ground
45:1, 45:10, 45:11, 47:3, 47:4, 47:11, 48:2, 50:18, 51:1, 51:5, 51:10, 51:22, 52:1, 52:16, 53:4, 53:6, 53:22, 54:9, 55:2, 55:8, 55:9, 55:12, 55:21, 56:7, 56:8, 57:14, 57:15, 59:3, 60:3, 60:12
grounds
29:16, 40:2
group
11:12
groups
11:19
grown
9:5
growth
19:12, 19:13

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00071

gs
26:11
guess
12:15, 17:13, 54:14, 59:4

H

half-hour
45:8
hand
64:31
handful
50:4
happen
34:19, 53:12, 53:16, 55:18
happens
53:14, 54:1, 54:10, 58:10
happy
17:20
head
34:22
help
18:21, 27:5, 31:20, 48:13, 49:2
here
5:21, 7:3, 8:7, 25:22, 29:20, 33:3, 36:17, 36:19, 37:10, 37:13, 38:19, 41:14, 46:13, 63:1
hereby
64:4
hereinbefore
64:5
hereunto
64:30
high
15:18, 32:14, 42:18, 43:19
highlighted
51:3
hits
26:4
however
33:1
hug
47:21, 48:9, 48:16, 48:20, 48:22, 49:8, 49:11, 49:18
hug's
48:3
huge
19:15, 42:22
human
33:4, 34:1
hybrid
27:8
hybridize
24:9, 49:9, 49:18
hybridizing
24:6, 36:2

I

idea
36:13, 56:12
ideal
20:22
identical
20:8
identification
6:3, 21:7, 32:18, 38:11
identifier
41:5, 48:13, 51:14, 52:2, 52:6, 52:19, 53:1, 53:5, 55:3, 55:6, 55:11, 55:17, 58:3, 58:11, 62:2
identify
62:12
identity
36:21
image
24:4
imagine
11:16, 20:19, 35:13
implement
37:7
implementation
50:5
import
26:2
inc
1:5, 1:8, 3:4, 3:13, 64:12
include
46:19, 52:19, 55:14, 58:6, 59:1
included
50:13
includes
23:10, 33:19, 52:18, 55:10
including
6:21, 7:9, 52:10, 55:5
index
4:1
indicate
8:1
individual
7:11, 11:10, 12:10, 12:18, 12:19, 13:4, 13:14, 16:8, 30:9, 52:10, 53:2, 56:22
individually
10:19
inference
59:5
information
11:5, 12:19, 13:13, 13:19, 14:10, 14:15, 14:18, 16:20, 17:10, 38:3, 40:12, 42:20
informing
25:7
initial
28:22, 29:2, 53:11, 53:15, 55:19, 58:8
initiate
26:14
input
9:17, 19:20, 20:10, 24:3, 24:14, 27:12, 34:10, 41:6, 48:14, 50:8, 53:2
inside
7:13
instead
58:6, 58:10
institution
59:11, 59:17
interested
64:25
internet
54:5
internet-connect-ion
56:6
interrupt
38:5
intrinsic
20:1, 36:22
introducing
61:6, 61:10
introductory
45:22
involve
12:17, 30:14, 57:6
involved
49:21
involves
55:3
ipr
1:11, 5:14
irreplaceable
39:4
itself
61:12

J

job
1:24

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00072

joining
5:11
joshua
3:6

K

karen
1:26, 2:7, 64:2, 64:38
keep
6:15
keeps
41:6
key
22:11, 23:10
kind
10:20, 14:20, 16:9
kinds
7:19, 57:10, 57:11
klerekoper
1:26, 2:7, 64:2, 64:38
know
5:17, 9:8, 12:1, 12:4, 12:5, 16:9, 16:11, 16:13, 19:3, 20:7, 20:9, 20:19, 21:13, 23:13, 23:18, 25:2, 25:3, 25:20, 27:1, 27:11, 29:1, 29:19, 29:21, 34:19, 35:14, 37:5, 39:14, 39:21, 40:16, 42:16, 42:19, 43:15, 44:5, 45:3, 48:13, 51:14, 51:19, 52:17, 55:15, 56:17, 59:8, 59:13, 59:19
knowledge
45:18, 47:17, 48:7, 49:7, 61:8
known
53:19

L

lab
7:6
label
26:21
labeled
24:17
labels
31:20
lag
22:20
laird
39:5, 39:18, 40:11
language
57:4
laptop
22:20
large
19:7
last
7:10, 15:21
later
15:17, 27:20, 47:19
lead
19:15
least
19:5, 21:14, 45:12, 46:6, 47:15, 47:20, 61:13, 62:19, 62:20
lee
39:5, 39:19, 40:11
legend
26:22, 27:18, 44:13
less
34:11
let's
36:19, 37:10, 37:13
level
7:14, 15:18, 15:19, 16:11, 17:22
levels
52:9
libraries
48:14
library
42:6, 42:7, 42:8, 44:1
ligate
49:16, 51:16, 53:10, 56:18, 58:7, 58:15
ligated
32:12, 51:9
ligating
51:13, 51:14, 53:5, 54:12, 55:3, 58:20, 59:7
ligation
46:7, 47:15, 48:4, 48:12, 48:18, 48:21, 49:1, 49:4, 53:14, 54:1, 54:9, 57:6, 58:10, 61:10, 61:13
limitation
47:13
lines
33:3
link
6:5, 17:5
linker
48:3, 49:8, 49:15
linkers
48:20, 49:18
linnarsson
4:14, 11:22, 21:3, 21:6, 21:8, 22:9, 22:10, 23:11, 23:16, 23:17, 23:20, 28:3, 28:7, 28:11, 30:11, 30:15, 30:16, 30:20, 32:2, 32:6, 32:16, 41:15, 42:17, 43:6, 43:22, 44:5, 44:10, 44:11, 44:18, 45:18, 45:22, 47:7, 48:6, 50:10, 50:17, 52:7, 53:8, 54:12, 54:19, 57:16, 59:6
linnarsson's
21:11, 22:6, 22:16, 29:14, 30:3, 46:19, 50:22, 58:16, 58:21, 59:2, 60:4
little
6:12, 7:15, 11:20, 16:10, 21:3, 21:4, 22:20, 26:20, 27:7, 52:15, 55:8
llp
3:7, 3:15
loaded
16:10
look
6:7, 6:17, 10:12, 11:17, 11:18, 13:17, 13:18, 15:3, 16:5, 17:8, 21:10, 21:13, 32:16, 36:18, 37:11, 38:6, 62:12
looked
16:7, 16:17, 17:2, 32:6, 59:15

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00073

looking
7:20, 9:14, 10:18, 12:18, 13:8, 13:13, 14:6, 14:9, 15:1, 15:5, 38:7, 38:19, 39:15, 41:19, 42:13, 43:5, 46:12
looks
21:10, 33:22
lose
34:9
lot
7:6, 22:10
lots
16:12

M

machine
43:3
made
53:10, 53:14, 58:8
magnitude
19:16
main
10:21, 19:1
make
20:5, 29:1, 43:2, 43:18, 52:12, 58:6
making
27:10, 29:15, 43:13
manges
3:15
many
20:11, 34:19, 48:17
mapped
29:19
mapping
32:3
marked
6:3, 21:7, 32:18
marriage
64:23
material
34:20
materials
34:9
matter
57:10, 64:28
maximize
57:12
maybe
18:7, 21:21, 22:15, 42:2, 45:8, 60:16
mccloskey
4:15, 28:3, 32:17, 32:19, 33:8, 35:11, 35:21, 36:1, 36:19, 36:22, 37:20, 38:4, 38:6, 38:8, 38:13, 38:18, 38:19, 39:13, 41:4, 45:18, 46:1, 47:7, 48:6, 52:7, 52:13, 52:18, 53:18, 55:16, 56:15, 56:19, 62:1, 62:18
mccloskey's
36:7, 36:14, 46:18, 54:18, 60:6, 60:7
mean
7:2, 7:17, 9:3, 9:4, 9:12, 11:8, 16:5, 16:6, 17:13, 33:15, 36:16, 41:1, 60:13
meaning
53:1
measure
7:22
measuring
11:6
megan
3:5
mentioned
6:20
mentions
36:19
method
22:6, 22:16, 23:1, 23:5, 23:9, 23:12, 30:4, 36:1, 39:14, 46:1, 46:5, 49:4
methods
29:15, 36:8, 36:9, 36:14
michigan
2:8, 64:3, 64:39
micrograms
33:5, 33:9, 33:11, 33:13, 34:1, 34:2, 34:8, 34:14, 34:21, 35:6, 35:7
might
27:5, 32:15, 40:4
miner
37:17, 39:5, 39:18, 40:7, 40:10
minute
54:6
minutes
60:16
misspoken
33:22
mixed
34:2
mixing
34:17
modifies
57:15
modify
46:18, 47:5, 47:12, 52:12
molecular
7:6, 18:11, 18:19, 41:5, 51:14, 52:2, 52:6, 52:19, 52:22, 53:5, 55:3, 55:5, 55:10, 55:17, 57:1, 58:3, 58:11, 61:6, 61:10, 62:1
molecule
25:14, 48:3
molecules
19:17, 25:16, 32:11, 42:22, 43:12, 48:14, 50:9
more
14:18, 19:8, 20:18, 22:10, 31:21, 35:2, 42:4, 62:4
morning
5:12
morphology
13:8
mostly
49:3
motivated
46:18
move
45:1
moving
25:22, 29:8, 45:10
mrna
22:7, 24:3, 24:10, 24:13, 26:18, 27:11
much
60:20
multifunctional
52:8, 59:9
multiple
25:8, 40:12, 56:15, 56:19
myers
7:5

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00074

myself
55:8

N

name
5:8, 5:10
natural
54:20, 61:17
naturally
26:5
nearby
8:2
necessarily
13:9, 17:19, 28:7, 30:22
necessary
30:8, 31:10
neck
16:14
need
14:11, 42:22, 43:1
needs
57:9
neurological
7:7
neurons
7:11
never
14:21
next
8:18, 28:16, 41:12, 41:19
ngs
15:16
nonhumans
9:7
nontemplated
26:8
notary
2:8, 64:1, 64:3, 64:38
nothing
59:18
notice
2:7
nucleotides
24:13
number
7:8, 21:19, 50:1, 50:6
numbers
17:16, 19:17, 62:10, 62:13
nw
3:8

O

oakland
64:39
oath
5:2
objection
11:13, 12:14, 13:6, 14:1, 17:12, 21:17, 23:6, 27:16, 28:14, 34:6, 40:14, 42:14, 43:8, 57:18
obscures
8:12, 9:22
obtain
42:7
obtaining
43:22
obvious
28:4, 45:19, 46:1, 54:16, 59:5
obviously
22:9
obviousness
29:17, 30:5, 32:2, 40:3, 47:8, 47:9
occurred
64:16
october
64:33
odd
14:20
office
1:1
oh
41:21, 59:18
okay
5:16, 6:10, 6:14, 7:15, 8:6, 8:7, 9:2, 10:10, 10:22, 13:2, 13:17, 14:4, 15:3, 15:15, 17:3, 18:1, 18:19, 21:2, 21:20, 22:22, 23:3, 23:21, 24:20, 25:18, 25:22, 26:16, 27:13, 28:16, 29:14, 30:19, 31:1, 32:15, 32:20, 33:3, 33:8, 33:13, 33:17, 33:21, 35:2, 35:4, 37:15, 37:20, 38:6, 38:15, 39:16, 40:10, 42:2, 42:11, 44:5, 45:4, 45:10, 45:15, 45:16, 46:13, 47:1, 51:5, 52:14, 52:21, 53:4, 53:13, 54:22, 56:12, 57:17, 58:9, 60:10, 61:16, 62:6
oligo
35:15
oligonucleotide
24:6, 26:10, 34:13, 35:20, 58:15, 58:20
oligonucleotides
35:4, 35:8
oligos
33:19, 34:18, 48:13, 49:2, 49:22, 50:1
one
7:4, 10:16, 11:18, 12:5, 13:2, 13:20, 14:18, 15:1, 19:6, 19:14, 19:18, 20:10, 24:19, 24:22, 25:8, 28:6, 28:10, 29:7, 29:16, 29:22, 30:6, 31:3, 35:2, 35:12, 35:16, 35:19, 42:17, 46:7, 47:15, 48:9, 48:16, 48:22, 49:1, 49:4, 49:21, 50:3, 50:16, 51:12, 52:4, 55:10, 56:16, 57:6, 58:3, 58:5, 60:1, 61:13, 61:16, 62:15
only
38:22, 42:19
open
6:7, 7:21, 7:22
opinion
16:2, 24:21, 25:7, 28:3, 31:8, 43:5, 45:11, 45:17, 48:6, 52:3, 55:9, 57:14, 57:15
opinions
23:16, 29:6, 30:4, 32:2, 39:20
optimize
57:8
optional
23:14, 28:9, 30:6, 30:11, 31:5
optionally
23:9
options
50:16

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00075

orders
19:16
ordinary
47:18, 48:7, 51:21
organisms
9:18
original
8:4, 18:2, 26:18, 41:11, 45:13
originally
8:8, 35:5
other
25:1, 25:3, 27:17, 28:5, 28:15, 31:17, 37:16, 38:1, 48:10, 48:15, 49:16, 49:19, 57:7, 62:15
others
23:15, 25:7, 49:6
otherwise
64:25
out
12:1, 16:14, 19:19, 25:16, 31:17, 32:13
outcome
64:27
over
7:9, 7:10, 15:21, 57:16, 57:19
overall
22:9, 57:12
owner
1:9, 3:12

P

page
4:3, 4:10, 6:12, 8:4, 8:5, 8:8, 8:9, 15:4, 18:2, 18:3, 22:1, 32:21, 38:14, 38:18, 38:22, 39:12, 41:11, 41:12, 41:13, 45:12, 45:13, 45:14
pages
1:25, 42:3
pair
42:20
panel
26:22, 27:5
paper
37:5
paragraph
6:11, 6:16, 6:19, 7:3, 7:18, 8:3, 8:7, 8:19, 9:3, 15:3, 15:17, 18:1, 18:5, 18:8, 18:10, 37:10, 37:12, 37:14, 37:18, 38:8, 39:1, 39:9, 41:10, 41:17, 45:16, 45:21, 45:22, 46:13, 46:15, 54:11, 58:14, 58:19, 62:10, 62:13, 62:14, 62:16, 62:17, 62:18
paragraphs
21:13, 37:8, 38:1, 38:2, 47:20
parallel
12:11
parkway
3:16
parlance
55:16
parse
1:5, 3:3
part
23:19, 25:4, 25:18, 27:19, 27:21, 29:14, 30:3, 30:8, 30:10, 31:6, 32:5, 48:17, 53:17, 53:18, 59:20
particular
16:6, 22:18, 25:19, 29:20, 30:8, 31:11, 33:11, 34:8, 35:22, 43:3, 43:14, 49:1, 49:10, 50:5, 57:9, 58:2
particularly
21:22, 41:4
parties
64:22, 64:24
parts
6:8, 52:18
party
64:12
patent
1:1, 1:3, 1:9, 1:12, 3:12, 28:4
pathways
8:13
patient
9:6, 38:10
pcr
19:3, 20:1, 21:1, 28:22, 29:4, 36:9, 37:1, 37:7, 37:19, 41:9, 53:12, 53:15, 61:17
people
15:20
per-cell
10:20
percent
34:11
perfect
6:18
perform
19:2, 21:1
performed
8:14
performing
9:19, 10:2, 11:17, 14:12
performs
60:5, 60:7
perhaps
21:9, 25:7, 45:11
person
5:13, 47:17, 48:7, 48:19, 51:21, 54:17
pertinent
11:5, 31:7
petitioner
1:6, 3:3
phd
1:15, 2:2, 4:5, 5:4, 64:4, 64:16, 64:26
phrase
7:18, 12:13, 13:22, 16:10
piece
59:7
pieces
29:13
place
38:21, 38:22
planet
3:21
platform
43:14
please
5:9, 18:2, 18:5, 28:19, 29:9, 32:8, 45:3, 56:11, 62:12
point
8:15, 12:16, 26:3, 27:9, 37:8, 42:21, 43:1, 45:2, 47:2, 47:3, 53:8
poly-a
24:5, 24:9
polynucleotide
46:6

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00076

polynucleotides
30:20, 47:14, 61:12
portion
40:18, 41:1, 56:16, 60:5
portions
60:5
posa
45:19, 46:17, 49:5
posita
60:3
position
30:19
possible
48:17
pr
24:7
practiced
15:6
prepared
43:12
preparing
15:13, 43:11, 43:18
present
3:20, 10:14, 36:6
preserving
16:20, 17:10
pretty
60:17
primarily
52:11
prime
24:4, 26:4, 27:2, 42:7, 44:1, 44:6, 44:14, 44:18
primer
24:6, 26:8, 26:13, 36:4, 37:7, 49:14, 49:15, 50:7
primers
25:21, 28:22, 29:2, 36:9, 49:16, 50:4
prior
18:12, 18:20
probably
14:19
problem
18:11, 18:17, 19:1, 19:21, 37:2, 37:18, 41:8, 51:16, 53:3, 53:20, 54:5, 62:5
proceeding
63:2
process
9:14, 19:13, 22:9, 26:7, 28:6, 30:12, 33:19, 41:7, 53:8, 55:19, 56:21, 57:12, 61:18
processed
42:6
processing
12:4
products
31:16, 37:1
profound
16:1
projects
7:9
property
11:19
protocol
49:1
provided
17:6, 49:22
provides
48:22
providing
40:12, 57:22
public
2:8, 64:1, 64:3, 64:38
published
42:18
pull
21:21, 32:21
pulled
33:1
pure
31:21
purposes
48:15
pursuant
2:7
put
20:4, 31:22, 32:11, 34:11, 41:6, 42:22
putting
53:9

Q

question
12:16, 13:11, 55:1, 56:7
questions
60:21, 61:1, 61:5, 62:21
quickly
45:5, 60:17
quite
11:14, 13:10, 17:1, 57:14
quote
41:14, 41:20, 42:4, 42:5, 43:4, 46:4
quotes
39:10

R

range
36:10, 36:15
raymond
3:5, 4:6, 5:7, 5:17, 6:15, 21:21, 56:4, 60:15, 60:19, 63:1
reaction
19:10, 26:14, 46:7, 47:15, 61:14
reactions
34:12, 59:22
read
5:2, 26:21, 32:13, 59:11, 59:14, 59:21
reading
61:22
readout
20:9, 30:18
readouts
10:13, 11:1
really
16:1
recall
16:19, 16:22, 21:18, 22:3, 22:17, 30:7, 31:3, 31:8, 32:3, 35:13, 36:17, 39:21, 40:10, 44:2, 44:17, 50:14, 59:16, 59:22, 60:2, 60:8, 61:4, 61:19
recalling
44:16
received
6:5
recently
7:7, 39:1
recognition
27:19, 27:21
recommending
39:13
record
5:9, 56:3, 60:16, 60:18, 64:9
reduce
18:21, 20:14, 62:2
reducing
18:8, 18:17
redundancy
20:6, 36:22, 37:4, 40:17, 40:22
redwood
3:16, 3:17

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00077

reference
21:5, 22:16, 33:4, 37:17, 47:21
references
15:8, 15:12, 15:16, 17:1, 17:3, 37:16, 39:19, 40:20, 46:17, 46:20
referring
18:16, 39:8, 46:14
refers
42:5
reflected
34:20
regard
61:9
regarding
29:16
regardless
20:10
region
46:20
regulate
7:13
regulating
8:1
regulatory
7:12, 9:15, 10:15
reich
3:6
related
7:10, 25:21, 43:17, 64:21
released
32:11, 44:6, 44:19
relevant
41:4, 43:10, 47:8
reliance
21:3
relied
29:22, 30:1
relies
48:20
rely
8:10, 21:10, 23:15, 24:20, 25:6, 28:2, 28:5, 28:12, 29:5, 29:15, 30:4, 32:1, 40:2, 48:2
relying
30:7
remains
44:14
remember
27:5, 39:22, 40:5, 40:15, 40:19, 44:4, 44:21, 62:10
remembering
44:12
remotely
64:16
rendering
31:8
renders
28:4, 45:19, 46:1
repeated
50:7
repeating
55:8
report
5:14, 5:20, 9:21, 10:4, 11:8, 12:13, 13:22, 14:14, 15:4, 15:13, 15:17, 17:15, 17:20, 21:4, 21:5, 21:12, 21:15, 21:19, 25:9, 28:12, 30:2, 31:2, 36:12, 37:9, 38:7, 40:5, 40:8, 41:11, 44:3, 51:2, 51:18, 53:14, 58:9, 59:3, 59:20, 62:7, 62:9
reported
1:26
reporter
58:18, 64:1, 64:2
representation
22:5, 23:8
representations
25:4
represented
64:12
require
14:17
required
52:5
requires
53:20
resolution
17:16
respect
43:4, 44:8, 44:9, 61:14
rest
17:18
restriction
49:10, 49:13, 50:11, 50:15, 51:1
result
32:10
results
8:12
reverse
23:1, 24:11
review
15:12, 39:18
reviewed
39:22
rick
7:5
right
5:22, 8:5, 8:22, 11:22, 15:1, 17:1, 21:16, 24:15, 24:22, 25:10, 28:13, 28:17, 30:14, 33:6, 34:3, 44:21, 45:12, 45:13, 45:19, 46:12, 46:21, 47:6, 47:16, 49:8, 49:11, 52:19, 55:1, 55:11, 55:22, 56:5, 56:8, 57:3, 57:4, 57:20, 62:21
ringing
22:17
rna
26:5, 27:8
rounds
20:20, 20:21
routine
51:20
row
24:3
rpr
1:26
rt
24:12, 26:3
rule
20:17
run
13:20, 35:19
running
14:3

S

s
15:7, 15:20
said
13:12, 14:13, 41:18, 54:11, 56:9, 57:2, 60:2, 61:16
same
15:4, 19:19, 35:8, 43:6, 43:18, 58:1
sample
9:17, 10:12,

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00078

11:4, 12:1, 13:18, 16:21, 17:11, 27:12, 31:21, 33:9, 35:22, 36:20, 38:10, 38:11, 38:12, 38:20, 39:10, 40:11, 57:22
samples
8:20, 9:2, 9:3, 9:6, 9:7, 39:4
say
8:9, 8:11, 8:18, 9:2, 9:11, 9:22, 10:5, 10:12, 14:13, 15:5, 16:14, 18:4, 18:11, 20:6, 20:20, 21:9, 36:7, 40:21, 52:22, 54:6, 54:15, 58:22, 59:14, 59:19
saying
16:7, 17:14
says
27:2, 38:9, 39:3, 44:13, 46:4, 58:14, 61:12
scenario
20:19
schemes
49:20
screen
5:18, 21:22, 32:22, 42:2, 42:3
scroll
5:21
se
16:15, 29:22, 31:9, 32:3
second
12:6, 13:3, 26:15, 26:17, 42:5, 46:20, 52:5, 58:4, 58:16, 58:20, 59:1, 60:6
section
37:11, 45:12, 46:21, 47:19, 62:8
sections
62:20
see
5:22, 6:22, 8:16, 11:21, 15:10, 18:14, 21:12, 22:22, 25:11, 33:1, 33:3, 33:7, 36:19, 37:10, 37:13, 38:16, 38:22, 39:6, 41:14, 41:16, 41:17, 41:18, 42:1, 42:4, 42:9, 46:3, 46:4, 46:22, 47:21
self
50:2
self-annealing
34:16
send
29:3
separate
12:10, 25:16, 31:17
separated
12:1
separately
11:9
sequenase
34:3
sequence
30:20, 31:17, 35:15, 52:17, 54:12, 58:16, 58:21, 59:1, 59:9
sequencer
31:22, 32:12, 32:14, 43:3, 43:20
sequences
18:12, 18:20, 60:4
sequencing
6:22, 7:3, 7:17, 7:18, 9:21, 10:3, 10:9, 10:13, 12:9, 14:6, 14:7, 14:8, 15:22, 16:4, 30:14, 30:17, 42:19, 43:13, 43:14, 43:19, 48:14
series
24:7, 28:9, 31:5, 48:10, 49:22
serve
52:9
set
36:5, 49:6, 64:5, 64:30
setups
57:11
several
7:10
share
11:19
shores
3:16, 3:17
short
42:7, 43:22
shorthand
64:1
should
6:7, 14:13
show
23:4, 23:22, 28:20, 31:13
showing
24:2, 25:20, 26:17, 27:6, 27:8, 31:14, 32:9
shown
5:21, 27:15, 28:16, 32:8, 43:6
shows
23:8, 26:1, 29:9
side
24:15, 25:10
signature-mig2k
64:34
similarly
52:13
since
15:7, 17:2, 26:20
single
9:8, 9:11, 9:13, 10:2, 10:5, 10:7, 10:18, 10:22, 13:1, 13:19, 14:21, 15:6, 16:18, 17:17, 38:11, 39:4, 55:15, 57:22
single-cell
6:21, 7:3, 7:14, 7:16, 7:18, 8:19, 8:21, 9:20, 10:3, 10:9, 11:7, 11:11, 11:16, 12:9, 12:12, 12:17, 12:21, 13:5, 13:12, 13:15, 13:21, 14:8, 14:14, 14:17, 16:3, 16:4, 17:22, 22:22, 38:20, 39:10, 39:15
site
8:1, 15:8, 27:19, 27:21, 50:14, 50:20
sites
31:19

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00079

sitting
36:17
sizes
19:11
skewed
62:2
skill
47:18, 48:7, 48:19, 51:21, 54:17
slowly
19:8
small
17:16, 19:8, 19:13
smaller
29:12
solve
18:11, 41:8, 51:15
solves
53:2
solving
18:16, 53:19, 62:5
some
7:9, 11:10, 11:19, 12:3, 17:17, 19:6, 22:11, 23:10, 23:18, 27:9, 42:21, 43:1, 52:18, 61:5
something
12:5, 12:6, 12:8, 45:8, 53:6
sorry
33:21, 34:5, 37:4, 37:22, 38:5, 40:7, 41:21, 46:10, 46:13, 54:2, 54:4, 54:6, 55:7, 55:12
sort
7:16, 10:16, 24:3, 24:11, 28:10, 28:21, 31:16, 42:3, 45:21, 47:2, 49:12, 51:5, 54:22, 57:7
sound
21:16
sounds
11:14, 13:16, 14:22, 60:9, 60:14
source
38:10
sources
9:18
species
9:9, 9:12
specific
14:11, 29:19, 36:2, 39:13, 40:2, 48:16, 56:14, 57:2
specifically
40:1, 43:15, 44:8, 50:20, 58:15, 62:18
specified
36:20
specifies
35:10, 38:9
split
42:3
st
64:31
stage
20:9
stamp
5:21, 35:8, 35:11, 35:16, 36:20, 38:9, 55:16, 60:6
stamped
6:12, 8:5, 8:9, 18:2, 22:1, 32:21, 38:14, 41:12, 45:14
standard
64:18, 64:19
start
10:8, 45:21, 47:11, 57:19
started
19:19, 34:7, 56:9
starting
47:2, 47:3, 62:18
starts
37:12, 39:1, 45:16, 57:16, 62:14
state
2:8, 5:8, 48:17, 61:9, 64:3, 64:39
statement
45:17
states
1:1, 44:6, 44:18
stating
45:22
step
18:13, 18:21, 20:14, 23:21, 24:12, 25:15, 25:22, 26:7, 27:1, 28:16, 28:22, 29:20, 30:6, 30:8, 30:11, 31:11, 31:15, 32:1, 32:3, 33:15, 34:16, 52:5, 58:2
steps
22:11, 22:14, 23:8, 23:14, 23:15, 28:9, 30:14, 31:5, 34:15
stick
16:14, 24:9
sticky
49:12
still
12:15, 20:21, 52:14, 57:13
stipulation
5:2
stone
3:7
str
23:12
strand
25:11, 26:15, 26:16, 26:17, 26:18
strategy
49:12
street
3:8
strt
22:16, 23:4, 23:9, 23:14
stuck
44:14
style
56:15, 56:19
subsequent
30:13, 34:12, 53:12
subsequently
29:3
suggest
14:22
suitable
43:2, 43:13, 43:19
suite
3:8
super
26:21
sure
5:10, 7:4, 9:22, 10:10, 11:14, 54:3, 54:8, 62:14
switching
26:9, 27:1
sworn
5:4, 64:6
sydorick
3:21
synthesis
55:19, 55:20

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00080

T

tag
20:4, 20:6, 20:13, 20:18, 20:22, 22:6, 24:15, 41:5, 52:5, 52:13, 53:1, 53:20, 55:4, 55:15, 56:15, 56:18, 56:19, 57:1, 58:4, 58:16, 58:21, 59:1, 59:9, 60:4, 61:6, 61:10, 61:12, 62:2
tagged
22:22, 33:14, 46:5, 47:13
tagging
20:3, 33:8
tags
18:11, 18:20, 20:8, 20:20, 46:19, 51:9, 52:8, 52:9, 55:5, 55:10
tail
24:5, 24:9
take
32:16, 45:3, 45:6, 49:14, 53:8, 62:12
taken
52:16, 64:8
takes
26:7
taking
31:18, 36:3
talk
18:8, 19:2, 25:1, 38:3, 58:13, 62:17
talked
25:9, 27:14, 51:13
talking
11:15, 36:2, 36:8, 37:1, 39:9, 42:11
talks
25:2, 37:2, 38:1, 38:8, 39:3
target
18:12, 18:20, 36:4, 36:5
task
11:18
tasks
11:17
teaching
41:3, 46:18, 52:7, 53:18
teachings
54:18
tech
5:17
technical
56:2
technician
3:21
technique
48:12, 48:18
techniques
6:21, 8:10, 15:15
technological
15:19
technology
15:16
tell
7:2, 12:5, 17:9, 28:19, 29:9
template
19:7, 19:15, 19:18, 20:2, 20:4, 20:10, 26:9, 27:1, 36:4, 36:21, 37:3, 37:4, 40:17, 40:22
templates
19:5, 19:6, 19:8, 36:5, 36:11, 36:15, 41:6, 49:3, 52:10, 53:2
ten
15:21
term
7:17, 9:4, 9:10, 10:4, 11:7, 38:19
terms
16:6, 37:19, 62:4
testified
5:5
testimony
64:9
text
25:2
th
3:8
thank
5:11, 5:19, 27:13, 60:19
thanks
5:11
themselves
50:3
theory
48:2, 51:5, 51:8, 55:3, 60:11
thing
27:17, 43:11, 51:15, 54:20
things
7:21, 27:20, 31:18, 61:16
think
7:19, 9:9, 11:16, 11:21, 13:7, 13:12, 14:2, 14:11, 14:21, 16:7, 20:19, 23:10, 23:12, 24:18, 33:21, 35:10, 38:21, 39:11, 39:12, 42:15, 43:9, 44:3, 44:12, 46:12, 47:7, 49:20, 50:14, 50:15, 51:12, 52:4, 52:14, 52:16, 54:11, 54:16, 57:13, 58:13
thought
14:20
three
15:8, 20:20, 24:4, 27:2, 40:19, 44:1, 44:6, 44:14, 44:18
through
8:8, 21:14, 22:14, 23:21, 23:22, 33:18, 37:13, 37:14, 38:3, 41:7, 45:5, 46:6, 47:10, 47:14, 47:20, 53:8, 61:13, 62:19
throughout
21:11
throughput
32:14, 42:18, 43:19
time
8:15, 11:18, 15:2, 60:20, 64:18, 64:19
times
21:19
timing
54:15, 61:5, 61:9, 61:15
tissue
9:6, 10:12, 13:18
title
23:7
today
13:3, 13:20, 15:21, 22:21, 60:20

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00081

together
7:8, 49:17
tomorrow
13:4
top
24:3, 26:16, 34:22, 55:4
track
41:6, 48:13, 52:9, 53:2
trademark
1:1
traditional
8:9
transcript
64:26
transcription
23:1, 24:12
trial
1:3
true
64:8
try
11:20, 22:19
trying
12:7, 27:4, 45:5, 47:1, 51:6
ts
24:7
tso
26:19, 27:22, 51:10, 51:17, 52:1, 52:12, 52:17, 53:9, 54:13, 55:5, 55:9, 55:13, 55:14, 56:17, 58:7, 58:12, 58:17, 58:21, 59:2, 59:6, 61:6
tsos
22:6
turn
6:11, 8:3, 18:1, 21:3, 41:10
two
20:20, 29:16, 42:3, 55:10, 60:4
typically
14:21

U

uh-huh
40:9
ultimate
51:6
ultimately
34:17
umi
56:18
unclear
26:20, 27:7
understand
7:15, 12:7, 13:10, 47:2, 51:6
understanding
12:16, 54:17, 55:7, 57:14, 59:21
uneven
41:9
unique
16:20
united
1:1
units
50:7
universe
28:11, 48:17
use
11:7, 12:21, 21:4, 23:18, 26:13, 28:22, 41:5, 48:11
useful
25:15, 39:14, 50:5
uses
26:11
using
14:6, 22:6, 31:9, 31:15, 43:3, 50:6, 59:5

V

variable
50:1
variety
6:21, 9:18, 11:17
various
7:19, 12:20, 12:21
vary
8:12
verbiage
17:18, 58:4
version
24:19, 24:20, 52:13, 57:6
versus
10:9, 12:5, 15:20, 16:13, 19:15, 19:18
via
64:16
view
10:17, 13:5, 28:3, 45:18, 48:6
virtually
2:4

W

wait
41:17
walk
22:14
walter
3:14, 4:7, 11:13, 12:14, 13:6, 14:1, 17:12, 21:17, 23:6, 27:16, 28:14, 34:6, 40:14, 42:14, 43:8, 57:18, 60:22, 61:3, 62:21
want
6:7, 21:10, 21:13, 26:2, 45:2
wanted
46:15
washington
3:9
way
12:12, 13:21, 31:3, 37:6, 50:7, 60:1, 64:25
ways
12:20, 12:21
we'll
45:3, 45:6
we're
14:6, 40:16
we've
15:4
wednesday
1:17, 64:17
weil
3:15
wells
12:2
whatever
45:6
whereas
10:18
wherein
46:5
whereof
64:30
whether
8:1, 12:8, 12:9, 12:11, 16:5, 16:8, 16:19, 17:9, 27:4, 27:7, 27:8, 31:9, 40:10, 44:5, 44:15, 47:3, 55:2, 57:14, 57:16
whole
35:17, 35:19, 36:10, 36:15, 37:11, 46:8

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00082

widely
15:6
willing
59:18
within
22:10, 23:14, 24:1, 28:11, 30:11, 30:15, 30:16, 51:10, 55:5, 55:12, 58:7, 59:1, 64:3
without
10:14, 60:13
witness
4:3, 5:3, 34:5, 64:5, 64:9, 64:30
word
59:15
work
7:6, 7:9
worked
15:20
working
55:1
worth
34:19
wouldn't
13:9, 57:7, 59:14
written
37:6
wrong
46:13
wrote
5:13, 16:17, 17:14, 17:20, 51:17
wu
3:7

X

xxxx
27:3

Y

yeah
10:10, 24:17, 33:2, 34:7, 36:20, 39:11, 44:2, 44:4, 44:12, 45:9, 45:15, 46:11, 48:22, 52:22, 58:14, 62:19
years
7:10, 15:22
yourself
6:8

Z

zoom
54:4, 64:16

.

.27
34:2, 34:14, 35:7
.3934
3:18
.5878
3:10

0

00876
1:11, 5:14

1

1)(f)(ii)
46:21
10
1:8, 3:12, 6:12, 33:5, 62:19, 64:12
10,155,981
1:12
1002
4:13, 5:18, 5:22, 6:3
1003
4:14, 21:6, 21:7, 21:22
1004
4:15, 32:17, 32:18
1006
17:3
101
38:1, 38:2
1013
40:8
102
38:1
103
38:1
1032
17:3
1033
17:4
104
38:3, 62:19
1050
3:8
108
45:12, 45:14
11
21:11, 21:18, 22:1, 22:2, 23:4, 23:7, 23:10, 23:19, 23:22, 24:1, 24:2, 26:1, 26:2, 27:15, 27:22, 28:2, 28:12, 28:17, 28:20, 29:5, 29:8, 29:9, 29:10, 29:18, 31:4, 31:12, 31:13, 32:5, 32:8, 42:11, 42:13, 42:15, 43:7, 43:16, 44:8, 44:9, 44:13, 50:13, 50:21, 63:2, 64:18
110
21:13
113
21:14, 45:14
117
21:14
12
6:16, 6:19, 46:21
13
6:11, 41:15, 41:22
139
21:14
140
21:14
166
21:14
17
3:8
176
38:8, 39:9
19
41:18
198
41:10, 41:17

2

2.7
34:8
2.71
33:4, 33:9, 33:11, 33:13, 33:22, 34:20, 35:5
20
1:17, 20:21, 63:2, 64:17, 64:18, 64:27
20006
3:9
201
3:16
202.505
3:10
2023
1:11, 1:17, 5:14, 64:17, 64:27, 64:31
2024
64:33
21
4:14, 41:15, 41:22, 64:31
23
1:17, 64:17,

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00083

64:27
235
45:16, 45:21
237
46:14, 58:14,
58:19
240
47:20, 54:11
242
47:20
25
41:15, 41:22
28
41:18

3

300
42:20
32
4:15, 8:4,
41:18
33
8:8
37
8:5
38
8:9

4

40
18:2
4250
1:26
45
18:3

5

518804
1:24
56
1:19, 64:17

6

60
22:1
61
4:7
63
1:25
650.802
3:18

7

73
8:3
74
8:19, 9:3
75
15:3, 15:17
762
38:13, 39:12

8

801
3:8

9

9
1:19, 64:17
90
15:7, 15:20,
34:11, 37:12,
37:13, 62:14
91
18:8
92
18:1, 18:4,
18:5, 18:10
93
37:14
94
41:11
94065
3:17
981
29:21, 30:9,
31:7, 32:4
99
41:12, 62:18

10x Genomics, Inc. Exhibit 2018
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00955
Page 00084