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Transcript of Peter Sims, Ph.D.

Date: June 26, 2025
Case: Integrated DNA Technologies, Inc. -v- Tecan Genomics, Inc. (PTAB)

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WORLDWIDE COURT REPORTING & LITIGATION TECHNOLOGY

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UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD
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INTEGRATED DNA TECHNOLOGIES, INC., Case IPR Nos:

IPR2024-01502
Petitioner, U.S. Patent 9,546,399
IPR2024-01504
U.S. Patent 11,098,357
-against- IPR2024-01506
U.S. Patent 11,725,241
IPR2025-00015
TECAN GENOMICS, INC., U.S. Patent 10,036,012
IPR2025-00016
Patent Owner. U.S. Patent 10,876,108
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DEPOSITION of PETER SIMS, PH.D. taken by the Patent Owner, pursuant to Notice, held at the law offices of Williams Connolly 650 5th Avenue, Suite 1500 New York, NY 10019, on June 26, 2025, at 9:15 a.m., before a Notary Public of the State of New York.
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ALSO PRESENT:
MICHAEL LEVY- Danaher

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EXHIBITS

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P E T E R S I M S, the witness herein, having been first duly sworn by a Notary Public of the State of New York, was examined and testified as follows:

THE REPORTER: Please state your name for the record.

THE WITNESS: Peter Sims, M.D.

THE REPORTER: Please state your address for the record.

THE WITNESS: 54 Pine Street Ardsley, New York 10502.

MS. CIPRIANO: Hi. I'm Linnea Cipriano, counsel for patent owners in this case. With me is Timothy Beavers and -- and, yeah, just with me is Timothy Beavers.

MR. FLETCHER: Tom Fletcher, Williams & Connolly LLP, for the petitioner, Integrated DNA Technologies. With me are my colleagues, Kevin Hoagland-Hanson and Anna Searle. Also present is Mike Levy from Danaher.

EXAMINATION BY
MS. CIPRIANO:
Q. Good morning, Dr. Sims.

5

1 **A. Good morning.**
2 Q. My name is Linnea Cipriano, as I said, and I'm
3 going to be asking you some questions today and possibly
4 tomorrow.
5 Have you ever been deposed before?
6 **A. I have been deposed before.**
7 Q. How many times?
8 **A. I have been deposed twice.**
9 Q. Okay. And when were those approximately?
10 **A. Yeah, approximately two years ago and then one**
11 **earlier this year.**
12 Q. And the deposition two years ago, was that --
13 were you serving as an expert in that matter?
14 **A. I was serving as an expert witness in that**
15 **matter.**
16 Q. And what was the subject matter of that case?
17 **A. It's related to single-cell sequencing.**
18 Q. And who were you retained by in that matter?
19 **A. The law firm was Wolf Greenfield. They're**
20 **representing Scale Biosciences.**
21 Q. And in the deposition earlier this year, what
22 was the subject matter of that case?

6

1 **A. That deposition was related to the same case.**
2 Q. Okay. And that was a patent case?
3 **A. It is a patent case.**
4 Q. Okay. And are you representing the patent
5 holder or the accused infringer?
6 MR. FLETCHER: Objection.
7 Q. Excuse me. Let me rephrase that question.
8 Have you been retained by the patent holder or
9 the accused infringer in that case?
10 **A. I have been retained by the patent holder in**
11 **that case.**
12 Q. So I'm sure this deposition will be a lot like
13 your previous two depositions, but let's go through some
14 ground rules so we're on the same page. I will being
15 asking you questions, and your answers today will be
16 under oath. And that oath is the same as you would take
17 as if you were testifying in court.
18 Do you understand that?
19 **A. I understand that.**
20 Q. And during the course of the deposition, your
21 counsel may make objections, but unless you've been
22 instructed by counsel not to answer, I'm expecting you

7

1 to answer my questions to the best of your ability.
2 Do you understand that?
3 **A. I understand that.**
4 Q. As you probably noticed, we have a court
5 reporter taking down everything we say today. And so
6 that means that you and I have to be careful not to
7 speak over one another.
8 Is that fair?
9 **A. Completely understand.**
10 Q. So I will try to wait for you to finish your
11 answer, so please wait for me to try to finish my
12 question.
13 We'll take breaks from time to time, but I
14 would ask that we don't take a break while there's a
15 question. If you could answer my question before we
16 take a break, and then we can take a break at your
17 convenience?
18 Do you understand?
19 **A. I understand.**
20 Q. And along those same lines, if you need a
21 break, please just let me know. I'm happy to take a
22 break whenever.

8

1 **A. I will let you know.**
2 Q. I will ask you to listen carefully to my
3 questions. I'm sure that my questions will not always
4 be clear. So if you have any -- if there's any
5 confusion, please ask me to clarify and I will try to do
6 so.
7 Is that fair?
8 **A. That is fair.**
9 Q. But if you answer my question, I'm going to
10 assume that you understood it.
11 Is that also fair?
12 **A. That is fair.**
13 Q. Okay. And you understand that, while I'm
14 asking questions during the deposition, when the
15 deposition is over, you are not permitted to discuss the
16 substance of your testimony with your attorneys.
17 Do you understand?
18 **A. I understand.**
19 Q. Is there any reason that you would not be able
20 to answer my questions fully and truthfully today?
21 **A. There is no reason.**
22 Q. Did you prepare for today's deposition?

9

1 **A. I prepared for today's deposition.**
2 Q. And without revealing any privileged
3 communication with your counsel, at a high level, what
4 did you do to prepare for this deposition?
5 **A. I reviewed my declaration, I reviewed**
6 **references in my declaration, and I met with counsel.**
7 Q. Did you speak to anyone besides counsel in
8 preparation for this deposition?
9 **A. I did not speak to anyone besides counsel in**
10 **preparation for this deposition.**
11 Q. And when did your preparation -- when did your
12 meetings with counsel occur?
13 **A. All of my meetings related to preparation for**
14 **this deposition occurred in the month of June of this**
15 **year.**
16 Q. And approximately how many hours did you spend
17 preparing?
18 **A. I would guess probably about 40 hours.**
19 Q. There's a lot of material here. I understand.
20 **A. Indeed.**
21 Q. You said you reviewed some documents in your
22 preparation for the deposition; is that accurate?

10

1 **A. That is accurate.**
2 Q. Besides your declaration, do you recall
3 specifically what documents you looked at?
4 **A. I looked at the Iafrate patent application;**
5 **that's Exhibit 1011 in my declaration. I looked at a**
6 **research article by Kivioja, et al.; that's Exhibit**
7 **1012. I looked at a patent application by Bielas,**
8 **Exhibit 1013. There may have been a few others, but**
9 **those are three that I paid particular attention to.**
10 Q. Now, you prepared two declarations in
11 connection with the proceedings that are at issue,
12 correct?
13 **A. I prepared two declarations. So the materials**
14 **that I just described are related to my declaration on**
15 **the '399, '357, and '241 patents.**
16 Q. Understood. Understood.
17 So just to get it out of the way, let's just
18 get in front of you both declarations and confirm that
19 those are accurate copies. We'll only be looking at one
20 for a little bit, but just for the logistics --
21 MR. FLETCHER: Counsel, we gave him
22 bound copies so they don't fall apart or get

11

1 lost.
2 Q. Okay. So if we look at the exhibit marked
3 1079, do you have that?
4 **A. I have that.**
5 Q. And is Exhibit 1079 the declaration that you
6 submitted in IPRs 2024-01502, '1504, and '1506?
7 **A. That is correct.**
8 Q. And if you turn to the last -- last page of the
9 exhibit before the Exhibit A at the back, that's on the
10 page marked 0327 at the bottom corner.
11 **A. I see that.**
12 Q. Is that your signature?
13 **A. That is my signature.**
14 Q. Okay. And if you could just look at the
15 other -- other declaration -- let's pause.
16 Exhibit 1079, that relates to, just for the
17 record, U.S. Patents 9,546,399, 11,098,357, and
18 11,725,241, correct?
19 **A. That is correct.**
20 Q. Okay. And then if we look at Exhibit 1085 in
21 IPRs 2025-00015 and '0016, do you have that in front of
22 you?

12

1 **A. I have that in front of me.**
2 Q. Is Exhibit 1085 the declaration that you
3 submitted in these proceedings? The referenced
4 proceedings on the face of the document?
5 **A. That is correct.**
6 Q. And then on the page in Exhibit 1085, at the
7 bottom of -- bottom right-hand corner is marked 0206?
8 **A. I see that.**
9 Q. Is that your signature?
10 **A. That is my signature.**
11 Q. So throughout the deposition, typically we'll
12 be talking about one declaration or the other, but there
13 are sections of the declarations that are either
14 identical or very similar.
15 Is that fair?
16 **A. There are sections of the two declarations that**
17 **are very similar.**
18 Q. Okay. So I'll do my best to point out where
19 they're similar and where they're different, but to the
20 extent the concepts -- particularly the background
21 concepts are the same and I refer to Exhibit 1079, to
22 the extent that paragraph also appears in Exhibit 1085,

13

1 would your testimony still be the same as far as the
2 background concepts?
3 **A. For background-related statements in the two**
4 **declarations that are the same, my testimony and**
5 **opinions would be the same.**
6 Q. Great. Thank you.
7 And to the extent there would be differences
8 between the two proceedings, please let me know and I'll
9 try to alert you to that.
10 **A. Okay.**
11 Q. So at a high level, how did you prepare these
12 declarations?
13 **A. I met with counsel many times. I researched**
14 **prior art references and background references. I**
15 **didn't do all the typing in these declarations, but I**
16 **ensured that they accurately represent my opinions in**
17 **this case.**
18 Q. You said you researched prior art references.
19 Did you identify independently any of the prior art that
20 is cited in your declaration?
21 **A. I identified some of the references, including**
22 **prior art references, that are cited in my declaration.**

14

1 Q. And do you recall, sitting here today, which
2 references you identified?
3 **A. I particularly recall identifying Exhibit**
4 **1013 -- this is in my declaration, Exhibit 1079 -- a**
5 **patent application by Bielas. I likely identified some**
6 **of the other background-related references, but I don't**
7 **completely recall the details. It was a while ago.**
8 Q. Understood.
9 As part of preparing your declarations, did you
10 consult with anyone other than the attorney team?
11 **A. I did not.**
12 Q. Have you reviewed any of the documents that
13 have been submitted in connection with the litigation
14 that is associated with these patents?
15 **A. I don't recall reviewing any of those**
16 **documents.**
17 Q. Okay. So since submitting your declaration,
18 you understand that there's been -- or do you understand
19 there's been correspondence from patent owner and also
20 from the board in these proceedings?
21 **A. I'm aware of those communications.**
22 Q. Okay. Have you read patent owner's preliminary

15

1 responses?
2 **A. I have read patent owner's preliminary**
3 **responses.**
4 Q. And in connection with the '00015 and '0016
5 proceedings, did you read Dr. Bustamante's declaration?
6 **A. I have read Dr. Bustamante's declaration.**
7 Q. Is there anything in the patent owner's
8 preliminary response that changes or makes you want to
9 amend your opinions in your declaration?
10 **A. Nothing I read in the patent owner's response**
11 **makes me want to change my opinions that are laid out in**
12 **my declaration.**
13 Q. Same question for Dr. Bustamante's declaration.
14 Anything in that make you want to change or amend your
15 declaration?
16 **A. Nothing in Dr. Bustamante's declaration changes**
17 **my opinions as laid out in my declaration.**
18 Q. Do you know Dr. Bustamante?
19 **A. I know Dr. Bustamante by reputation. I don't**
20 **know that I've met him in person.**
21 Q. And what is that reputation, in your view?
22 **A. He's a successful and reputable scientist in**

16

1 **the field of genomics, particularly computational**
2 **genomics.**
3 Q. Have you read the Patent Trial and Appeal Board
4 panel's institution decision in these matters?
5 **A. I have read the PTAB decision in these matters.**
6 Q. Much easier to say.
7 Is there anything in the institution decisions
8 that you -- that would make you change your opinions or
9 positions in your declarations?
10 **A. Nothing in the PTAB decision documents changes**
11 **my opinions as laid out in my declarations.**
12 Q. Okay. Are there any corrections or edits that
13 would you like to make to your declarations sitting here
14 today?
15 **A. None that I've encountered so far.**
16 Q. Okay. Understood. There's always that stray
17 typo, right?
18 So let's turn to -- if you could turn to
19 Exhibit A in -- it's my -- from my comparison, it's the
20 same in both declarations, but we can look at the one
21 that's in Exhibit 1079. And that's -- on the page at
22 the bottom, it's marked 3290329.

17

1 A. **Yes.**
2 Q. Are you there?
3 A. **Yes, I'm there.**
4 Q. This is -- is this your CV?
5 A. **This is my CV.**
6 Q. Is it accurate?
7 A. **It is accurate. It is very slightly out of**
8 **date, but it is accurate.**
9 Q. Okay. And what changes would need to be made
10 to make it up to date?
11 A. **It's just missing a few of my recent**
12 **publications from 2025.**
13 Q. You are currently employed, correct?
14 A. **I am currently employed.**
15 Q. And what is your current position?
16 A. **I am an associate professor at Columbia**
17 **University, and I am the scientific director of the**
18 **Columbia Genome Center.**
19 Q. And what do you consider your area of
20 expertise?
21 A. **My area of expertise is genomics, including**
22 **technology development and applications of genomics,**

18

1 **mostly in the areas of cancer biology and immunology.**
2 Q. So you gave two titles in your current -- in
3 your current roles. If we just think about your role as
4 an associate professor at Columbia. What is -- what
5 does that entail?
6 A. **It entails two main things. One is teaching,**
7 **mentoring, and training students, and the other is**
8 **performing research.**
9 Q. And what is that area of research?
10 A. **My lab's research focuses on genomic technology**
11 **development mostly with applications in cancer biology**
12 **and immunology.**
13 Q. And when you say "genomic technology
14 development," what do you mean by that?
15 A. **We develop tools, both experimental and**
16 **computational, for interrogating the genomes and**
17 **transcriptomes of cells -- mostly human cells.**
18 Q. Mostly genome cells?
19 A. **Mostly human cells.**
20 Q. Human cells.
21 And can you explain the difference between
22 experimental tools and computational tools?

19

1 A. **Experimental tools means that we are working at**
2 **a wet bench with cells, with genetic material, DNA and**
3 **RNA, and performing measurements on those materials.**
4 **Computational tools means that we're developing**
5 **algorithms and computer programs for analyzing the data**
6 **that arises from those measurements.**
7 Q. In your current genomic work, do you use
8 next-generation sequencing?
9 A. **We make extensive use of next-generation**
10 **sequencing.**
11 Q. And which platforms do you typically use in
12 your lab?
13 A. **Currently, my lab uses sequencers manufactured**
14 **by Illumina and Element Biosciences.**
15 Q. Okay. So you also said you were the
16 scientific -- apologies if I get this -- scientific
17 director of the Genome Center? Is that --
18 A. **That's correct.**
19 Q. Okay. What is your -- what does your role
20 entail in that position?
21 A. **The Genome Center at Columbia is a core**
22 **facility that performs experiments and computational**

20

1 **analysis on a fee-for-service basis for other**
2 **investigators at Columbia and also some external**
3 **investigators. I supervise the staff in that facility.**
4 Q. And then I'm guessing that also does a lot of
5 next generation sequencing in that facility?
6 A. **The Genome Center does a lot of next generation**
7 **sequencings.**
8 Q. And what platforms are used in that facility?
9 A. **That facility uses sequencing instruments**
10 **manufactured by Illumina and Element Biosciences.**
11 Q. Now are they the same instruments that you use
12 in your lab, in your research or are they separate?
13 A. **My lab does almost all of its sequencing in the**
14 **Columbia Genome Center.**
15 Q. So I'd like to talk a little bit about your
16 training and your educational -- I'm going to refer to
17 paragraph 5 of your declaration of the Exhibit 1079, but
18 feel free, if you need to look anywhere else -- I doubt
19 that you need to look somewhere for your background, but
20 just to let you know where I am, I'm on paragraph 5.
21 So you explained that you worked on NGS, excuse
22 me, can we agree that NGS stands for next-generation

21

1 sequencing?
2 **A. I completely agree.**
3 Q. Okay. You explained that you worked on NGS
4 technologies during your Ph.D. training; is that
5 correct?
6 **A. I worked on NGS technologies during my Ph.D.**
7 **training.**
8 Q. And could you please explain what your Ph.D.
9 work focused on?
10 **A. The beginning of my Ph.D. work focused on**
11 **single-molecule biophysics. I was studying motor**
12 **proteins. Towards the end of my Ph.D. training, I**
13 **started to actually build a next-generation sequencing**
14 **platform in the lab.**
15 Q. So you finished your Ph.D. in 2009.
16 Approximately when did that building of an NGS platform
17 begin prior to 2009?
18 **A. I began that work in 2007.**
19 Q. And what did that work entail?
20 **A. That work entailed organic synthesis of**
21 **fluorescently labeled nucleotides. It involved**
22 **developing microfluidic devices and constructing a**

22

1 **microscopy system.**
2 Q. Did you publish any work on that NGS platform
3 that you worked on?
4 **A. I did. That research is reported in a paper**
5 **that's actually Number 90, publications Number 90 in my**
6 **CV. You can see it on 1079.0339.**
7 Q. Okay.
8 **A. First author Sims. It's entitled "Fluorogenic**
9 **DNA Sequencing in PDMS Microreactors."**
10 Q. Was that system ultimately used anywhere
11 besides the lab you worked in?
12 **A. A version of that system is commercially**
13 **available in China.**
14 Q. So if I did the math right, you published two
15 other papers in the same timeframe as that -- the paper
16 Number 90 in your CV, but I'm specifically looking at
17 papers 89 and 88 on your list that were published in
18 2012.
19 Do you see those?
20 **A. I see those.**
21 Q. Is that work that you did as a post-doc or as a
22 grad student?

23

1 **A. I think I probably started working on both**
2 **projects towards the end of my Ph.D., but the bulk of**
3 **the work was done during my post-doctoral period which**
4 **was between 2009 and 2011.**
5 Q. So when you started on building the NGS
6 platform in 2007, had you done any DNA sequencing
7 projects before then?
8 **A. I don't think I had done any DNA sequencing**
9 **related projects before then. I had used DNA sequencing**
10 **on occasion, but not in the capacity of technology**
11 **development.**
12 Q. Understood.
13 In your current role, you teach classes; is
14 that correct?
15 **A. I teach classes.**
16 Q. Okay. And doing a little bit of research, one
17 of those classes is called deep sequencing; is that
18 accurate?
19 **A. I teach a course called deep sequencing.**
20 MS. CIPRIANO: Okay. If we could look
21 at -- we'll mark this as Exhibit 2022.
22 (Whereupon, BINF G4017 Deep Sequencing

24

1 Syllabus was marked as Exhibit 2022, for
2 identification, as of this date.)
3 BY MS. CIPRIANO:
4 Q. So the court reporter has just handed you a
5 document that we've marked as Exhibit 2022.
6 Do you recognize this Exhibit?
7 **A. I actually do not recognize this document, but**
8 **I believe that it's real and I recognize some of its**
9 **content very well.**
10 Q. Okay. If we look at the second page of the
11 document, that's your name and your picture?
12 **A. That's my name and a very old picture.**
13 Q. The name of the course, BINF G4017 deep
14 sequencing, is that the name of the course that you
15 teach?
16 **A. That's the name of the course that I teach.**
17 Q. And if you can look at the course description,
18 does this appear to be the syllabus or the reading
19 material assigned for the deep sequencing course that
20 you teach?
21 **A. This is the syllabus for the course that I**
22 **teach.**

25

1 Q. At a general level, what does this course
2 cover?
3 **A. The course is a graduate-level introduction to**
4 **the field of genomics. It's a very broad course.**
5 Q. So if we look at the section of text underneath
6 the pictures that starts on the second page of the
7 document, it's a little difficult to navigate the way
8 they printed it out, apologies for that.
9 But if I -- if we look at -- there's a section
10 called "Topics" that's underlined and there's a
11 little -- further down there's a section called "Goals"
12 that's underlined.
13 Do you see that?
14 **A. Mm-hmm. Yes.**
15 Q. And then a little bit further down there's
16 requirements?
17 **A. I see that.**
18 Q. Okay. And then onto the next page, following
19 the same convention, there's an introduction to
20 high-throughput sequencing technologies.
21 Do you see that?
22 **A. I see that.**

26

1 Q. And then there's Sims in parenthesis?
2 **A. I see that.**
3 Q. Am I interpreting it that this the first
4 lecture of the course, at least according to this -- I
5 guess, I'll say before, Introduction to High-throughput
6 Sequencing Technologies, there is a lecture 109/05.
7 **A. Introduction to High-throughput Sequencing**
8 **Technologies is the title of the first lecture.**
9 Q. Okay. And have you given that lecture in this
10 course before?
11 **A. I give that lecture when we teach this course.**
12 Q. And then there are two more underlined lecture
13 titles, throughout the document; it's Lecture 2,
14 Experimental Techniques For Genomics.
15 Do you see that?
16 **A. I see that.**
17 Q. And then Lecture 3, Technologies for
18 Transcriptomics -- if I am pronouncing that correctly --
19 and Regulatory Genomics.
20 Do you see that?
21 **A. I see that.**
22 Q. And each of those have a reading list after the

27

1 name of the lecture; is that accurate?
2 **A. That's right.**
3 Q. Did you select the articles that were assigned
4 reading for the lectures you gave in this course?
5 **A. I selected those articles.**
6 Q. And how did you go about selecting the articles
7 for these lectures?
8 **A. Some of the articles are selected because I**
9 **think they are of particular historical importance to**
10 **the way in which the field developed.**
11 **Some of the articles I chose because of my**
12 **personal familiarity with them, making me more**
13 **comfortable in teaching about them.**
14 Q. And some of these articles touch on concepts
15 in -- for next-generation sequencing, correct?
16 **A. Most of these articles are related to**
17 **next-generation sequencing.**
18 Q. And -- so when looking at the experimental
19 techniques for genomics, that lecture, what types of
20 experimental techniques do you touch on in your lecture?
21 **A. That lecture focuses on methods for sequencing**
22 **DNA in particular.**

28

1 Q. And what kinds of methods for sequencing DNA?
2 **A. Methods including whole genome sequencing and**
3 **exome sequencing.**
4 Q. What do you mean by "exome"?
5 **A. The exome is the part of the genome that**
6 **encodes exons, many of which are present in mRNA**
7 **transcripts that encode for protein, but not all.**
8 Q. And when you're making reference to
9 experimental techniques, are you talking about
10 experimental techniques or computational techniques?
11 **A. I would say that this lecture focuses on**
12 **experimental techniques, but alludes to computational**
13 **methods. Some of our experimental techniques are**
14 **designed with an -- analytical approaches in mind making**
15 **sure that the measurements are compatible with our**
16 **computational capabilities.**
17 Q. And can you give an example of something like
18 that that you talk about in your lecture?
19 **A. Exome sequencing is a good example. In exome**
20 **sequencing one limits the amount of data generated to a**
21 **small fraction of the genome, and that makes it easier**
22 **for computational methods to sensitively detect, for**

29

1 **example, mutations.**
2 Q. And why does limiting something to a small
3 section of the genome allow for sensitively detecting
4 mutations?
5 **A. Exome sequencing requires fewer sequencing**
6 **reads to gain sufficient coverage of the exome for**
7 **sensitively detecting mutations; and so it is more**
8 **tractable to very deeply sequence the exome from an**
9 **economic standpoint than to deeply sequence the entire**
10 **genome.**
11 **Although, I will say that sequencing costs are**
12 **decreasing really fast and this will not be true for**
13 **much longer.**
14 Q. Understood.
15 MS. CIPRIANO: Okay. You can put that
16 to the side.
17 Q. So in paragraph 7 of your declaration, you
18 state:
19 "I have frequently developed and
20 employed library construction and computational
21 methods for single-cell analysis that
22 incorporate UMIs."

30

1 And that's the last sentence of -- or
2 the most of the last sentence of paragraph 7.
3 Do you see that?
4 **A. I see that.**
5 Q. When you refer to UMI in this sentence, what do
6 you mean?
7 **A. UMI stands for unique molecular identifier.**
8 **I'm referring to a broad class of methods for**
9 **identifying, for example, PCR duplicates in a -- among**
10 **sequencing reads.**
11 Q. And you say it's a "broad class." Can you give
12 me some examples of instances where you've incorporated
13 UMIs?
14 **A. In my own research, I most frequently**
15 **incorporate UMIs for single-cell sequencing experiments.**
16 Q. And when you say "incorporate UMI," what --
17 what is the UMI that you are referring to when you say,
18 "incorporated into UMI single-cell sequencing
19 experiments"?
20 **A. It is very application specific, but we**
21 **frequently define a unique molecular identifier using a**
22 **combination of a molecular tag, which is a DNA sequence,**

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1 **and information from a target sequence such as its**
2 **alignment position on the genome.**
3 Q. Now, have you used UMIs outside the -- sorry.
4 Let me start over.
5 You've said that you most frequently
6 incorporate UMIs for single-cell sequencing experiments.
7 Do you use UMIs for any other type of
8 sequencing experiments?
9 **A. I have used UMIs for other experiments where we**
10 **were not sequencing individual cells, but we were**
11 **sequencing from a sample that was really small, and so a**
12 **lot of amplification was required to construct a library**
13 **for sequencing.**
14 Q. And so, in that context, are UMIs particularly
15 helpful when a lot of amplification is required to
16 construct a library for sequencing?
17 **A. UMIs are very helpful when a lot of**
18 **amplification is required.**
19 Q. And why is that?
20 **A. Amplification can lead to certain types of**
21 **artifacts that are readily corrected by UMIs -- by**
22 **analysis of UMIs.**

32

1 Q. And what do you mean by "artifacts"?
2 **A. Amplification can bias the relative proportion**
3 **of certain nucleic acid fragments in a sequencing**
4 **library. And during PCR, DNA polymerase can make**
5 **mistakes in copying DNA that leads the incorporation of**
6 **mutations.**
7 Q. So I'd like to break that down and make sure
8 that we're speaking the same language.
9 When you say bias the relative proportion of
10 certain nucleic acids in the sequencing library, what do
11 you mean, and what happens in that bias?
12 **A. In a PCR reaction, some nucleic acid fragments**
13 **might be amplified more efficiently than others even**
14 **though their relative proportion in the original sample**
15 **might be very similar.**
16 Q. And the other example you gave was that DNA
17 polymerase can make a mistake in copying DNA.
18 What happens there to cause -- to cause
19 problems?
20 **A. When DNA polymerase extends a primer, it**
21 **incorporates nucleotides one at a time, and occasionally**
22 **it will incorporate the wrong nucleotide -- for example,**

33

1 **one that is not complementary to the corresponding base**
2 **in the template strand.**
3 Q. So that creates an error, correct?
4 **A. We often refer to those as errors -- for**
5 **example, substitution errors.**
6 Q. But do all DNA polymerases used in DNA
7 sequencing and amplification cause these errors?
8 **A. Some are better than others, but to my**
9 **knowledge, all of them cause errors with some frequency.**
10 Q. And would you agree that the concept that DNA
11 polymerases cause errors in -- in copying DNA, that
12 concept was known by 2011?
13 **A. That concept was known by 2011.**
14 Q. Okay. So I'd like to turn to some of the
15 background that you set forth in your declaration. And
16 here we're -- many of the paragraphs I'm going to be
17 talking about are in the first chunk of the substance of
18 your declaration starting at paragraph 19. But just so
19 we're on the same page -- and I don't know if it you've
20 done the comparison, but we tried to.
21 Paragraphs 19 through 96 appear to be the same
22 in both declarations? If you could just page through

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1 and confirm.
2 **A. They appear to be very similar, if not**
3 **identical.**
4 Q. Okay. After -- after paragraph 96 in Exhibit
5 1079 and 1085, I think there's a difference for after --
6 if I talk about paragraphs after that, I'll try to make
7 sure that I'm specific in which declaration I'm talking
8 about. But just so we're on the same page, if I refer
9 to a paragraph before 96 or between 19 and 96, can we
10 agree that it applies to both declarations?
11 **A. I'm fine with that.**
12 Q. Okay. So for ease of reference, I'm going to
13 be looking at the declaration that's Exhibit 1079, just
14 so we're on the same page.
15 So starting at paragraph 19, you have a section
16 entitled "Legal Standards."
17 Do you see that?
18 **A. I see that.**
19 Q. And these were provided by counsel; is that
20 accurate?
21 **A. These were provided by counsel.**
22 Q. And does this section accurately set forth your

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1 understanding of the legal concepts at issue in these
2 proceedings?
3 **A. These reflect my understanding of the legal**
4 **concepts that are important to these proceedings.**
5 Q. And so if you could turn to paragraph 22, I'd
6 like to look at the second sentence of paragraph 22. It
7 says:
8 "In this regard, I understand that the
9 question for anticipation is what the POSA
10 would understand based on the teachings of the
11 prior art reference and not what the authors or
12 inventors of the prior art actually did in the
13 laboratory."
14 Do you see that?
15 **A. I see that.**
16 Q. What do you mean by "not what the authors or
17 inventors of the prior art actually did in the
18 laboratory"?
19 **A. For example, my understanding is that I am**
20 **supposed to read a piece of prior art and interpret that**
21 **prior art for myself based on what is written there.**
22 Q. So when you're talking about anticipation, if

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1 the authors or inventors of the prior art didn't do
2 something or didn't report something in their paper, is
3 your understanding that you can fill in those gaps?
4 MR. FLETCHER: Objection. Form.
5 **A. I think the key aspect of this statement is**
6 **POSA. A POSA is someone who has a breadth of experience**
7 **that allows him or her to interpret the prior art**
8 **drawing on that experience.**
9 **So, for example, in a research article, there**
10 **may be certain measurements that are taken, and a POSA**
11 **would understand what could be gleaned from those**
12 **measurements even when not explicitly stated. A**
13 **reference can teach certain aspects that can be gleaned**
14 **in light of the POSA's breadth of understanding.**
15 Q. So when you say "not what the authors or
16 inventors of the prior art actually did in their
17 laboratory," you're talking about the reasonable
18 inferences that a POSA would make based on the
19 disclosure; is that accurate?
20 MR. FLETCHER: Objection.
21 **A. Can you please repeat the question?**
22 Q. Sure. And I just want to -- what I'm getting

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1 at is I'm trying to understand what information -- what
2 information you're referring to by this "not what the
3 authors or inventors of the prior art actually did."
4 What information are you pulling in in addition
5 to actually what's on the paper or what they did in the
6 reference?
7 MR. FLETCHER: Objection.
8 **A. If the authors of a reference say that they**
9 **employed a specific technique, I know what information**
10 **can be gleaned from using that technique.**
11 Q. Okay. Thanks for that clarification.
12 So if we could turn the page and look at the
13 section that starts with paragraph 31, there's a section
14 that is titled "DNA."
15 Do you see that?
16 **A. I see that. I see that.**
17 Q. And then the next section, section B that
18 starts with paragraph 39, is a section that starts
19 "RNA"?
20 **A. I see that.**
21 Q. Would you agree that DNA and RNA serve
22 different functions in a cell?

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1 **A. DNA and RNA serve different functions in a**
2 **cell.**
3 Q. And what is the function of DNA? In a broad
4 sense? We could speak for days on that.
5 **A. DNA stores information about how to make and**
6 **regulate, for example, protein. RNA serves as a conduit**
7 **between the information on the genome and the synthesis**
8 **of protein, among other things.**
9 Q. So for reference, this is in -- I'm going to
10 refer to paragraph 33, but you could probably talk about
11 this in your sleep.
12 You agree that DNA contains coding and
13 non-coding regions, right?
14 **A. DNA codes -- I'm sorry. DNA contains both**
15 **coding and non-coding regions.**
16 Q. And what's the difference between coding and
17 non-coding regions?
18 **A. As stated in paragraph 33, coding regions**
19 **contain instructions for building cellular proteins, and**
20 **non-coding regions do not contain such information but**
21 **certainly regulatory functions.**
22 Q. And when you say, "serve regulating

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1 functions" -- or "regulatory functions," how -- can you
2 give me some examples of how that works?
3 **A. There are proteins called transcription factors**
4 **that regulate the transcription of coding regions. They**
5 **often bind to sequences in non-coding regions of the**
6 **genome in order to perform this function.**
7 Q. So when we think about the part of DNA that
8 encodes for -- let's just think about it as a single
9 protein, one gene.
10 The coding regions are not continuous in one
11 section; is that accurate?
12 **A. In higher organisms, like mammals, coding**
13 **sequences include both exons and introns. The exons are**
14 **often coding for protein. The introns are often removed**
15 **prior to protein synthesis. In lower organisms,**
16 **continuous coding regions are more common.**
17 Q. I appreciate that distinction. And I'll try to
18 be more specific in my questions.
19 So just to be clear, you say in higher
20 organisms, coding sequences include both exons and
21 introns, and those are interspersed with each other; is
22 that accurate?

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1 **A. That is accurate.**
2 Q. And so if you sequenced what we're talking
3 about -- one piece of DNA that includes both exons and
4 introns -- the resulting sequence would include both
5 sections that coded for proteins and sections that do
6 not code for proteins, correct?
7 **A. That is correct.**
8 Q. Are there reasons why a scientist would want to
9 sequence non-coding regions?
10 **A. There are many reasons. Non-coding regions**
11 **often contain important sequences for regulating gene**
12 **expression; as a result, mutations in non-coding regions**
13 **can have important effects on gene expression.**
14 Q. So when we refer to RNA, RNA is not just a --
15 let me step back.
16 There are many different types of RNA, correct?
17 **A. There are many types of RNA.**
18 Q. And what are the common types of RNA found in a
19 cell?
20 **A. In paragraph 40 of my declaration, there's a**
21 **non-exhaustive list that includes ribosomal RNA,**
22 **transfer RNA, and messenger RNA, but there are also many**

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1 **types of non-coding RNAs such as microRNAs.**
2 Q. So for the categories that you list here, what
3 is the function of ribosomal RNA in a cell? Let me
4 rephrase that question so we can be a little more
5 specific.
6 What is the function of ribosomal RNA in a
7 mammalian cell?
8 **A. Ribosomal RNA is an important structural**
9 **feature of the ribosome, but, importantly, it also**
10 **contains the catalytic domain of the ribosome; thus, it**
11 **plays a crucial role in the synthesis of protein.**
12 Q. And what is the role of transfer RNA in
13 mammalian cells?
14 **A. Transfer RNAs serve as a link between mRNA,**
15 **messenger RNA, and protein. They can interact with mRNA**
16 **in a sequence-specific manner, and they are also**
17 **attached to amino acids that are the building blocks of**
18 **protein. And so the ribosome uses transfer RNA in the**
19 **synthesis of protein from messenger RNA.**
20 Q. And what is the role of messenger RNA in
21 mammalian cells?
22 **A. The principal role of messenger RNA in**

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1 **mammalian cells is to present sequences from the genome**
2 **to the ribosome so that it can synthesize protein based**
3 **on that information.**
4 Q. And messenger RNA is often referred to as mRNA;
5 is that accurate?
6 **A. That is correct.**
7 Q. Is it accurate that the mRNA in a mammalian
8 cell only contains coding regions of genetic material?
9 **A. There are components of mRNA that do not encode**
10 **protein.**
11 Q. And what are those components that do not
12 encode protein?
13 **A. One component is the UTRs or untranslated**
14 **regions. They occur on the 3' and 5' ends of an mRNA.**
15 **Some MRNAs also have a poly(A) tail on their 3' end that**
16 **does not encode protein.**
17 Q. So other than the UTRs and the poly(A) tail,
18 does the rest of material of mRNA, does that represent
19 coding, genetic material?
20 **A. That is usually the case.**
21 Q. So -- and this probably confuses vocabulary,
22 but in simplest terms, mRNA does not include the introns

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1 that are in DNA in general, right?
2 **A. There is a molecule called pre-mRNA that**
3 **includes introns. Usually mRNA, in its mature form,**
4 **does not include introns, but not always.**
5 Q. Thank you.
6 And in your answer, I think you said that many
7 or most MRNAs have a poly(A) tail; is that accurate?
8 **A. Most MRNAs have a poly(A) tail in higher**
9 **organisms like mammals.**
10 Q. And what is the purpose of a poly(A) tail?
11 **A. This is a subject of active research, but the**
12 **poly(A) tail plays roles in mRNA stability and the**
13 **efficiency of protein synthesis from mRNA.**
14 Q. So in parts of your declaration, you refer to
15 the poly(A) region of mRNA as a homopolymer.
16 Do you recall that?
17 **A. I recall that.**
18 Q. What does the term "homopolymer" mean?
19 **A. A homopolymer is a nucleic acid sequence in**
20 **which the same nucleotide occurs more than once in a**
21 **row. For example, TTT would be a three-nucleotide**
22 **polymer.**

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1 Q. Is there an average length of a poly(A) tail?
2 **A. Poly(A) tails undoubtedly have an average**
3 **length. There have been many attempts to measure the**
4 **length of a poly(A) tail. To my knowledge, poly(A)**
5 **tails are typically on the order of a couple hundred**
6 **bases long.**
7 Q. Now, when you are looking to sequence mRNA,
8 would the goal or would one of the goals of that
9 sequencing be to sequence -- let me -- let me rephrase
10 my question to make it a little clearer.
11 Other than the specific study of poly(A) tails
12 when you're looking at the sequence of mRNA, do you
13 typically include the full poly(A) tail in the
14 sequencing library?
15 MR. FLETCHER: Objection.
16 **A. Some library construction methods result in**
17 **inclusion of long stretches of poly(A) tails in the**
18 **final sequencing library. Some methods do this on**
19 **purpose; sometimes it happens spuriously. There are**
20 **certain applications where the poly(A) tail is very**
21 **important.**
22 Q. And what are those applications where the

45

1 poly(A) tail is important?
2 **A. The poly(A) tail is very important for studies**
3 **that are attempting to assemble mRNAs from an organism**
4 **for which there is no reference transcriptome.**
5 Q. So let's break this down. How -- how do
6 studies assemble mRNAs when there is no reference
7 transcriptome?
8 **A. Studies that use next-generation sequencing for**
9 **transcriptome assembly, will often generate cDNA**
10 **libraries from mRNA, fragment those libraries, sequence**
11 **the resulting fragments and then use computer algorithms**
12 **that can make inferences about how those smaller**
13 **fragments were assembled in the original mRNA sample.**
14 **It's sort of like doing a puzzle.**
15 Q. And why is the poly(A) tail important in that
16 compilation?
17 **A. Going back to my puzzle analogy, detecting the**
18 **poly(A) tail is sort of like finding the corner piece.**
19 **You know that you're looking at the 3' end of an mRNA.**
20 Q. And how much of the poly(A) tail do you need to
21 know in your analogy that you have the corner piece?
22 **A. I haven't formed a carefully considered opinion**

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1 **on that subject, but one does not need to sequence the**
2 **entire poly(A) tail.**
3 MS. CIPRIANO: It might be good for a
4 quick break time.
5 MR. FLETCHER: Sure, we can go off the
6 record.
7 (Whereupon, a short break was taken.)
8 BY MS. CIPRIANO:
9 Q. Okay. So I'd like to turn -- we were talking
10 about RNA, and I'd like to talk a little bit about RNA
11 sequencing. And I'm looking at -- there's a section
12 entitled "RNA Sequencing" at paragraph 30 -- excuse me
13 paragraph 60 in your declaration.
14 **A. Okay.**
15 Q. But my questions are probably more general than
16 is necessary here. But you state:
17 "To sequence RNA, scientists use
18 reverse transcriptase to convert RNA into
19 cDNA."
20 Is that always required for RNA
21 sequencing?
22 **A. There are methods for direct RNA sequencing**

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1 **that do not require cDNA synthesis.**
2 Q. Do next-generation sequencing methods require
3 RNA to be converted into cDNA?
4 **A. It depends on how you define next-generation**
5 **sequencing. If one thinks of it as the generation of**
6 **sequencing technologies that came after Sanger**
7 **sequencing, there are two that come to mind in which**
8 **direct RNA sequencing has been reported.**
9 **There is a company called Helicos that no**
10 **longer exists, that developed a direct RNA sequencing**
11 **technology, and there is a company called Oxford**
12 **Nanopore that has developed a direct RNA sequencing**
13 **technology.**
14 Q. So for sequencing on the next-generation
15 sequencers that you talk about in your declaration,
16 specifically the 454, the Illumina and Ion Torrent,
17 would you need to convert RNA to cDNA to sequence on
18 those machines?
19 **A. To my knowledge, converting RNA into cDNA is**
20 **necessary for RNA sequencing on those instruments.**
21 Q. Excuse me. So I'd like to talk a little bit
22 about what you refer to as PCR.

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1 PCR stands for polymerase chain reaction; is
2 that accurate?
3 **A. PCR stands for polymerase chain reaction.**
4 Q. And so I'm looking at paragraph 71 and 72 of
5 your declarations. You explain two ways PCR can amplify
6 particular regions of genetic material.
7 Do you see that?
8 **A. I see that.**
9 Q. And in paragraph 71, you explain that you can
10 use primers designed to bind to known sequences in front
11 and behind of the portion that you want to amplify,
12 right?
13 **A. Paragraph 71 describes the use of primers,**
14 **specific to known sequences that are upstream and**
15 **downstream of the desired target.**
16 Q. And in your declarations, you explain that
17 there's a directionality typically assigned to portions
18 of nucleic acids; is that accurate?
19 **A. Nucleic acids have a 5' and a 3' end.**
20 Q. So when you say "upstream," that is toward the
21 5' end; is that accurate?
22 **A. It's a little tricky, because some nucleic**

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1 **acids are double-stranded and so --**
2 Q. Okay.
3 **A. -- upstream and downstream doesn't always mean**
4 **exactly that.**
5 Q. So just so we're on the same page, when you
6 refer to upstream and downstream in paragraph 71, that
7 is referring to areas of the nucleic acid that surround
8 or are on either side of a particular target region; is
9 that fair?
10 **A. Upstream and downstream regions might flank the**
11 **desired target region.**
12 Q. Is there a situation where they wouldn't flank
13 a desired target region?
14 **A. In some cases, the primers are complimentary to**
15 **sequences that are included in the target region, in**
16 **which case, those sequences are actually part of the**
17 **target region.**
18 Q. Okay. So in paragraph 71, the PCR that -- PCR
19 process that you're talking about there, that is using
20 two primers directed to sequences that are known; is
21 that accurate?
22 Let me clarify just one thing. So the PCR

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1 process that you're talking about in paragraph 71, that
2 is using two primers directed to sequences within the
3 genome that are known; is that right?
4 **A. Paragraph 71 makes no reference to a genome,**
5 **but it does refer to primers that are specific to known**
6 **sequences.**
7 Q. Okay. So let's put paragraph 72 in the mix
8 just because I think that it might make it easier to
9 talk about this in general.
10 Paragraph 72 talks about using PCR where
11 adapters have been ligated to the sequence, right?
12 **A. Paragraph 72 refers to ligation of adapters to**
13 **a sequence.**
14 Q. So to put paragraph 71 and 72 in context,
15 paragraph 71 could include scenarios where the primers
16 used in the PCR reaction are to known sequences on the
17 nucleotide that you are -- for the nucleic acid that
18 you're trying to sequence, right?
19 **A. Can you please repeat the question?**
20 Q. Yes, absolutely. I think I confused myself.
21 So paragraph 71, you talk about PCR with
22 primers specific to known sequences. And that can

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1 include scenarios where the primers are directed to
2 known sequences on the nucleic acid that you're
3 attempting to sequence, correct?
4 **A. The primers referred to in paragraph 71 can be**
5 **complimentary to known sequences on the nucleic acid**
6 **fragment that you were trying to sequence.**
7 Q. And in paragraph 72, you talk about the use of
8 adapters and -- I guess let's pause there, what do you
9 mean by "adapters" in paragraph 72?
10 **A. Adapters are typically synthetic**
11 **oligonucleotides with a known sequence that can be**
12 **incorporated into a library of nucleic acid fragments by**
13 **a variety of methods.**
14 Q. So in the PCR reactions that you are discussing
15 in paragraph 72, you say:
16 "PCR can also involve ligating adapters
17 with a phrase 'to both ends of each fragment.'"
18 So to think about it conceptually, you
19 have a sample full of fragments and the
20 adapters are introduced to basically stick
21 around both ends; is that accurate?
22 **A. Paragraph 72 refers to the ligation of adapters**

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1 **to either end of a set of nucleic acid fragments.**
2 Q. And if you're using adapters to facilitate a
3 PCR reaction, is it accurate that the goal would be that
4 all of the fragments get adapters attached to them?
5 MR. FLETCHER: Objection.
6 **A. That is not the case in every application.**
7 Q. Okay. And in what applications would you not
8 want adapters attached to all of the fragments in a
9 sample?
10 **A. There are many such situations. There may be**
11 **nucleic acid fragments in a sample that are not to be**
12 **sequenced or amplified in that sample, and so adapter**
13 **ligation to those sequences might be undesirable.**
14 **There are situations where certain nucleic acid**
15 **fragments may already have appropriate adapters attached**
16 **to them, in which case, adding additional ones would be**
17 **problematic for some reason.**
18 Q. After the section that you talk about -- after
19 the PCR section, you have a section that's included
20 "anchored PCR and genome mocking."
21 Do you see that?
22 **A. I see that.**

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1 Q. Now, these are sequencing technologies that
2 were in use before the development of next-generation
3 sequencing; is that accurate?
4 **A. That is correct. Many of the key references**
5 **are in the 1990s.**
6 Q. So in paragraph 76 of your declaration, you
7 refer to a paper by Siebert.
8 Do you recall that?
9 **A. I recall that.**
10 Q. And that describes a method you refer to as
11 "genome walking," right?
12 **A. That's right.**
13 Q. And then I'm looking ahead at page 78. As you
14 describe it, Siebert's method uses a single
15 gene-specific primer and a nongene specific primer to
16 target an unknown sequence.
17 Is that your understanding of what that paper
18 described?
19 **A. Siebert described methods for PCR amplification**
20 **of loci on the genome with both known and unknown**
21 **sequences.**
22 Q. And in that method of amplification described

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1 in Siebert, they used one gene-specific primer, correct?
2 **A. Siebert's method included the use of**
3 **gene-specific primers.**
4 Q. So in paragraph 78 you have a sentence:
5 "The authors then introduced a
6 gene-specific primer, white arrow below,
7 complementary to a known sequence in the
8 genomic DNA, white box below, and a primer with
9 the sequence of the longer 5' ligated adapter."
10 Do you see that?
11 **A. I see that.**
12 Q. And is it correct to interpret that you're
13 saying they used one gene-specific primer and one
14 nongene specific primer in doing the PCR amplification?
15 MR. FLETCHER: Objection.
16 **A. For amplification of a specific locus on the**
17 **genome, Siebert would use a gene-specific primer and an**
18 **adapter-specific primer.**
19 Q. And in the next sentence, paragraph 78, you
20 state that -- well, the sentence reads:
21 "The authors then used PCR with those
22 two primers to selectively amplify the unknown

55

1 genetic sequence between the adapter on one end
2 and the known genetic sequence on the other end
3 of each fragment."
4 Do you see that?
5 **A. I see that.**
6 Q. What do you mean by "selectively amplify" here?
7 **A. The authors were using PCR to cause**
8 **overrepresentation of certain sequences relative to**
9 **others in a sample.**
10 Q. And how was that accomplished in Siebert?
11 **A. Through Watson-Crick base pairing of the**
12 **gene-specific primer to a known genetic sequence, the**
13 **activity of DNA polymerase in the PCR reaction was**
14 **biased towards the sequence downstream of that primer.**
15 Q. Can you explain what you mean by "the activity
16 of the DNA polymerase in the PCR reaction was biased
17 towards the sequence downstream of that primer"?
18 **A. The design of the PCR reactions in Siebert made**
19 **it more likely that DNA polymerase would copy sequences**
20 **downstream of the gene-specific primer.**
21 Q. And when you're talking about the design of the
22 PCR reactions, the purpose of the primers here is to get

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1 DNA polymerase to bind to those sections and copy that
2 section of the nucleic acid; is that accurate?
3 **A. The purpose of the gene-specific primer is to**
4 **facilitate primer extension by DNA polymerase of the**
5 **sequence downstream of the primer.**
6 Q. So sequences in the sample that Siebert used
7 that did not have a sequence complementary to the
8 gene-specific primer would be less likely to be copied
9 in that reaction -- in that PCR reaction, correct?
10 **A. That is not strictly the case. There could be**
11 **sequences with partial complementary to the**
12 **gene-specific primer that are easy for the polymerase to**
13 **amplify that could also get copied efficiently.**
14 Q. So what about the design of the PCR reaction in
15 Siebert made it more likely that the DNA polymerase
16 would copy sequences downstream of the gene-specific
17 primer?
18 **A. Watson-Crick base pairing to the template**
19 **strand.**
20 Q. That's a concept that happens in -- in DNA
21 structure. That's not specific to Siebert's method,
22 right?

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1 **A. Watson-Crick base pairing is not specific to**
2 **Siebert's method, but he is leveraging that mechanism to**
3 **facilitate primer extension.**
4 Q. And so sequences in Siebert's sample that do
5 not bind to the gene-specific primer are less likely to
6 be copied in the PCR reaction that Siebert did, correct?
7 **A. I don't want to say less likely to be copied,**
8 **but PCR is designed to facilitate exponential**
9 **amplification. And, in Siebert, the concept is that the**
10 **combination of complementary to the gene-specific primer**
11 **and the adapter-specific primer facilitates exponential**
12 **amplification of certain nucleic acid fragments, but I**
13 **do not doubt that there are many nucleic acid fragments**
14 **that could also get copied to some extent in such a**
15 **reaction.**
16 Q. Understood.
17 So to clarify, the fragments in Siebert's
18 sample that contain both the sequence of the
19 gene-specific primer and the sequence of the adapter are
20 the fragments that will undergo exponential
21 amplification in the PCR reaction, correct?
22 **A. Those fragments will undergo exponential**

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1 **amplification.**
2 Q. And only those fragments will undergo
3 exponential amplification in Siebert's reaction; is that
4 accurate?
5 **A. I wouldn't make that claim because if Siebert's**
6 **input nucleic acids are from genomic DNA, there are**
7 **innumerate 3' ends in the sample that can hybridize all**
8 **over the place and facilitate primer extension. But**
9 **Siebert is attempting to amplify exponentially**
10 **particular sequences of interest.**
11 Q. All right. Let's -- I'd like to look at the
12 Siebert paper, and that's an exhibit that's already been
13 marked in these proceedings as 1007.
14 Do you recognize this exhibit?
15 **A. I recognize this exhibit.**
16 Q. And in preparing your declaration, did you
17 fully review this paper?
18 **A. I read the paper in preparing my declaration.**
19 Q. So at the beginning of the substance of the
20 article, it says:
21 "Several PCR base methods are available
22 for walking from a known region to an unknown

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1 region in cloned or uncloned genomic DNA. The
2 methods are of three types: Inverse PCR,
3 randomly primed PCR, and adapter ligation PCR."
4 Do you see that?
5 **A. I see that.**
6 Q. And then it goes onto say:
7 "However, these methods have not been
8 generally applied to walking in uncloned
9 genomic DNA because they are either complicated
10 or inefficient."
11 Do you see that?
12 **A. I see that.**
13 Q. Do you have an understanding of what the
14 authors were referring to as "complicated" and
15 "inefficient" in this sentence?
16 **A. I would probably need to read the other**
17 **references listed there to confidently interpret that**
18 **statement.**
19 Q. Okay. Do you have an opinion on whether
20 those -- the three methods that are listed in the
21 previous sentence -- inverse PCR, randomly primed PCR,
22 and adapter ligation PCR -- whether those are

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1 complicated or inefficient?
2 **A. I would want to read those references to**
3 **comment on that. I'm -- I -- I can't confidently answer**
4 **that question without looking at the papers carefully.**
5 Q. Okay. So you don't have an opinion on those
6 methods as you sit here today?
7 MR. FLETCHER: Objection.
8 **A. Yeah. I haven't formed a thoughtful opinion on**
9 **those methods.**
10 Q. So the next paragraph of Siebert discusses
11 variations on the known methods, it seems in my
12 interpretation. Just so we're on the same page, it
13 says:
14 "We have investigated the application
15 of long and accurate PCR to walking in uncloned
16 genomic DNA. We initially examined the use of
17 unpredictably primed PCR, a new method based on
18 randomly primed PCR, and Vectorette PCR, which
19 is based upon adapter ligation."
20 Do you see that?
21 **A. I see that.**
22 Q. Do you have an understanding of what is meant

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1 by "unpredictably primed PCR"?
2 **A. Again, that's among the references in the first**
3 **paragraph, and I'd need to read it to ensure that I can**
4 **accurately answer that question. I might surmise from**
5 **the phrase that comes after that it involves degenerate**
6 **primers.**
7 Q. Do you know what is meant by "Vectorette PCR"?
8 **A. I can probably guess based on the six-word**
9 **description that follows Vectorette PCR, but, again, I**
10 **would want to study the reference to answer that with**
11 **confidence.**
12 Q. Now, the method that Siebert used in his study,
13 he describes it as combining Vectorette PCR with a newly
14 developed method termed "suppression PCR."
15 Do you have an understanding of what the
16 combination of Vectorette PCR with suppression PCR
17 means?
18 **A. Based on my reading of Siebert, what's referred**
19 **to here is the use of adapter ligation and an approach**
20 **to depleting certain sequences during the course of a**
21 **PCR reaction.**
22 Q. So looking at the third full paragraph of

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1 Siebert, it says:
2 "In our hands, both unpredictably
3 primed PCR and Vectorette PCR generated
4 multiple PCR products even after nested PCR was
5 performed."
6 Do you see that?
7 **A. I see that.**
8 Q. Do you have an understanding of what nested PCR
9 is?
10 **A. There are many different implementations of**
11 **nested PCR. One example would be the use of more than**
12 **one forward primer in the amplification of nucleic acid**
13 **fragments.**
14 Q. And what is the purpose in nested PCR in the
15 example that you gave of having more than one forward
16 primer in the amplification of nucleic acid fragments?
17 **A. The objective of nested PCR is very application**
18 **specific. In some cases, nested PCR is used to enhance**
19 **the specificity with which certain target nucleic acids**
20 **are amplified.**
21 Q. And based on your understanding of that Siebert
22 article, is that the objective of nested PCR that

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1 Siebert applied?
2 **A. I would need to review this article more**
3 **carefully in order to confidently answer that question.**
4 **I haven't read this particular article in a while.**
5 Q. Given the statement that "In our hands, both
6 unpredictably primed PCR and Vectorette PCR generated
7 multiple PCR products even after nested PCR was
8 performed," you can't -- you don't have any
9 understanding of why nested PCR would impact the
10 instance that Siebert is talking about here?
11 **A. Can you remind me exactly where that sentence**
12 **is?**
13 Q. Yeah. It's the first sentence of the third
14 paragraph of the article.
15 **A. Let me read that.**
16 **My understanding of this paragraph is that**
17 **Siebert is referring to a nested PCR reaction that**
18 **generated multiple PCR products and some of these PCR**
19 **products were undesirable.**
20 Q. Do you have an understanding of why some of the
21 products were undesirable?
22 **A. This paragraph doesn't refer to any data that I**

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1 **can see, so there's very limited information here for me**
2 **to specifically comment. But Siebert may have been**
3 **attempting to amplify certain nucleic acid fragments,**
4 **and if some nucleic acid fragments that were not**
5 **targeted were also amplified, this could complicate**
6 **downstream analysis of the sample.**
7 Q. Is it fair to say that the nested PCR reference
8 in that first sentence of the third paragraph was an
9 attempt to reduce the undesirable PCR products in the
10 reaction?
11 **A. There's very little information about this**
12 **reaction described in the paper. A lot of times, when**
13 **the author refers to something that was done "in our**
14 **hands," they're often not showing the data or giving**
15 **sufficient detail. So having done a lot of PCR**
16 **reactions, I would want to look at those details myself**
17 **before making a strong claim about that.**
18 Q. Okay. In the next sentence, Siebert says:
19 "Although, upon analysis, some of the
20 PCR products were found to be derived from
21 successful walks, the presence of multiple PCR
22 products would complicate further

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1 characterization without Southern blot
2 hybridization or extensive cloning."
3 Do you see that?
4 **A. I see that.**
5 Q. And do you have an understanding of why the
6 multiple PCR products would complicate further
7 characterization?
8 **A. My understanding of that paragraph is that the**
9 **multiple PCR products, which would be mixed together at**
10 **the end of the PCR reaction, would require additional**
11 **purification processes to purify them from each other.**
12 Q. And what would be the need for the
13 purification?
14 **A. There are many possible applications of such**
15 **PCR products. For example, if one wanted to sequence**
16 **the PCR products in 1995, they would need to be pure.**
17 Q. Now was that still the case in 2011 with the
18 advancement of next-generation sequencing?
19 **A. Next-generation sequencing enables sequencing**
20 **from mixtures of nucleic acids.**
21 Q. Is there benefits in next-generation sequencing
22 to having a more pure sample?

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1 **A. This is entirely application-specific. There**
2 **are many cases where we try to make samples that have as**
3 **much breadth as possible, very complex mixtures of**
4 **nucleic acids; other cases where we might be interested**
5 **in particular nucleic acids.**
6 Q. So in instances where you're interested in
7 particular nucleic acids, are there benefits to the
8 sample being more pure for that particular nucleic acid?
9 **A. One benefit might be reduced cost.**
10 Q. Are there other benefits?
11 **A. Other benefits include higher coverage for the**
12 **purposes of mutation detection.**
13 Q. And what do you mean by "higher coverage"?
14 **A. Coverage is the number of reads that traverses**
15 **a specific nucleotide position.**
16 Q. Are there any other benefits that you can think
17 of?
18 **A. In certain app -- excuse me, in certain**
19 **applications, computational analysis of the resulting**
20 **data could be simpler.**
21 Q. Okay. So turning back to Siebert. Siebert
22 reports -- let me make sure I can find it.

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1 In the next paragraph, so it's the fourth
2 paragraph:
3 "We have improved upon the adaptor
4 ligation method by combining Vectorette PCR
5 with a newly developed method termed
6 'suppression PCR.'"
7 Do you have an understanding of how
8 Siebert's suppression PCR method works?
9 **A. During the PCR reactions described by Siebert,**
10 **certain nucleic acid fragments form hairpin structures.**
11 **He refers to them as panhandle structures, that reduce**
12 **the efficiency with which those nucleic acid fragments**
13 **are amplified.**
14 Q. So in the second page of Siebert, and I'm
15 looking at the third paragraph from the end in the
16 right-hand column, he states:
17 "We have found that the high
18 specificity of the method described is
19 primarily due to the suppression effect of the
20 adaptor/adaptor primer combination; although in
21 some cases additionally having an amine group
22 in the lower strand of the adapter (Vectorette

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1 blocking) yielded better results."
2 Do you see that?
3 **A. I see that.**
4 Q. So Siebert found that his PCR suppression
5 method was necessary to fix some of the non-specific
6 nature of the PCR reaction he used.
7 Is that fair?
8 **A. The suppression effect plays a role in the**
9 **specificity of the PCR reaction.**
10 Q. Well, Siebert said that the suppression effect
11 was the primary driver of specificity, right?
12 **A. I see that Siebert attributes the suppression**
13 **effect as the primary driver of the high specificity.**
14 **But a POSA would understand, and I'm sure Siebert would**
15 **understand that primer designer is very important as**
16 **well.**
17 **Siebert could have used primers that**
18 **facilitated a suppression effect and also gave poor**
19 **specificity.**
20 Q. Can you explain what you mean by that last
21 statement?
22 **A. What I think Siebert means here is that given**

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1 **the proper design of the primers and adaptors, the**
2 **suppression effect is really critical to the results**
3 **that were achieved. You could design this experiment so**
4 **that it wouldn't work very well also.**
5 Q. Understood. Understood.
6 MS. CIPRIANO: I'd like to look at
7 another paper, one that might be a little more
8 familiar with you. So we'll mark this as
9 Exhibit 2023.
10 MR. FLETCHER: Counsel, this is the
11 same as one of the exhibits cited in the
12 petition, I believe.
13 MS. CIPRIANO: It is?
14 MR. FLETCHER: Perhaps not. Perhaps
15 I'm mistaken, okay. Exhibit 2023?
16 MS. CIPRIANO: Well, let's
17 double-check. If it is, that was inadvertent.
18 THE WITNESS: I have removed my
19 glasses, so until it comes to me.
20 MS. CIPRIANO: Oh, is it?
21 MR. FLETCHER: I believe it's Exhibit
22 1030.

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1 MS. CIPRIANO: 1030?
2 MR. FLETCHER: Yeah, that's fine.
3 MS. CIPRIANO: Okay, then we don't need
4 to mark it. Sorry. It's just an oversight.
5 THE WITNESS: Oh, yeah.
6 MS. CIPRIANO: So it's a paper that's
7 already been marked Exhibit 1030. Thank you
8 for that catch.
9 BY MS. CIPRIANO:
10 Q. So do you recognize Exhibit 1030?
11 **A. I recognize Exhibit 1030.**
12 Q. And you were a coauthor of this paper; is that
13 accurate?
14 **A. I am a coauthor of this paper.**
15 Q. And at a high level, what is the focus of the
16 work recorded in this paper?
17 **A. The paper reports a barcoding and**
18 **next-generation sequencing strategy for accurate**
19 **quantification of RNA from a sample.**
20 Q. And the title starts with "Digital RNA
21 Sequencing."
22 Do you see that?

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1 **A. I see that.**
2 Q. What do you mean by "digital RNA sequencing"?
3 **A. There was an older technique called digital**
4 **PCR, that usually did not use sequencing as a readout.**
5 **But it was also useful for accurately quantifying**
6 **nucleic acids, and so we were drawing an analogy to**
7 **digital PCR in naming this method digital RNA**
8 **sequencing.**
9 Q. And so can you explain what digital PCR means?
10 **A. Digital PCR uses a method called limiting**
11 **dilution in which individual nucleic acid fragments are**
12 **distributed into containers, such that they can each be**
13 **amplified individually and separately from each other.**
14 **This serves to mitigate certain artifacts in**
15 **quantifying those individual nucleic acid fragments that**
16 **can occur when they're amplified together in a mixture.**
17 Q. And can you explain what you mean by
18 "artifacts"?
19 **A. For example, DNA polymerase might amplify some**
20 **molecules of DNA more efficiently than others. And in**
21 **certain applications, this is undesirable.**
22 Q. So I guess I don't quite understand your answer

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1 as it refers to the term "artifacts." How is the
2 amplification of certain molecules more efficiently than
3 others in artifacts in the context that you use that
4 term?
5 **A. In Figure 1A of the paper, there's a cartoon**
6 **illustration of what I mean. I'll use that to explain.**
7 Q. Okay.
8 **A. In this illustration, there's an original**
9 **sample that has three copies of cDNA molecule, a cDNA 1**
10 **and two copies of cDNA 2.**
11 **After amplification, there are nine amplicons**
12 **corresponding to cDNA 1 and 12 amplicons corresponding**
13 **to cDNA 2. So the relative abundance of those two cDNA**
14 **species is actually flipped. Now, cDNA 2 is more**
15 **abundant than cDNA 1, presumably because cDNA 2 was more**
16 **efficiently amplified; even though it was less abundant**
17 **in the original sample.**
18 Q. So if we're looking for a definition of the
19 term artifact as it's used in this context, would you
20 agree that it means an anomaly or an error in the data
21 that doesn't reflect the original sample?
22 MR. FLETCHER: Objection.

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1 **A. PCR can distort the relative abundance of**
2 **nucleic acid fragments, relative to their original**
3 **relative abundance in the sample.**
4 Q. So this difference in relative abundance is
5 that the only example that you would catalog as an
6 artifact of the process?
7 MR. FLETCHER: Objection.
8 **A. DNA polymerases used in PCR can also insert**
9 **substitution errors into PCR products. Sometimes they**
10 **make mistakes and incorporate the wrong nucleotide**
11 **during primer extension.**
12 Q. And that would also be termed an artifact?
13 **A. One could refer to those PCR-induced mutations**
14 **as artifacts or errors.**
15 Q. So you've given two examples of scenarios that
16 could be artifacts.
17 Are there any others that you can think of that
18 would be categorized as an artifact?
19 **A. PCR can lead to spurious recombination of**
20 **nucleic acids. So two nucleic acids that are not**
21 **attached to each other in the original sample might**
22 **become attached to each other during a PCR reaction.**

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1 Q. So is it fair to say that, if we're trying to
2 create a definition of the term artifact as you used it
3 in the term "mitigating certain artifacts," that it's
4 instances that occur in the final sample that is
5 sequenced that do not appear in the original sample?
6 MR. FLETCHER: Objection.
7 **A. Can you please repeat the question?**
8 Q. Sure.
9 Let me rephrase it and turn it around to you.
10 When I've asked for a definition of the term
11 artifact, you've given me certain examples. But can you
12 give me a definition of the term artifact as you used it
13 when talking about how digital PCR can mitigate certain
14 artifacts?
15 **A. The reference to digital PCR in this paper is**
16 **particularly related to the type of artifact shown in**
17 **Figure 1A.**
18 Q. Are you able to give me a definition of the
19 term artifact as you use it in your declaration and in
20 your work?
21 **A. If you can point me to a specific place in my**
22 **declaration where I used the word "artifact," I'm happy**

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1 **to try to clarify its meaning.**
2 Q. Well, you used it in reference to this paper.
3 Is that the only way that you use the term
4 "artifact" in your everyday work?
5 **A. It's not the only way what I use the term**
6 **artifact in my everyday work. It's a commonly used**
7 **phrase or term.**
8 Q. So in the way that you use it, in your everyday
9 work, what does it mean?
10 MR. FLETCHER: Objection.
11 **A. In the lab, we use a number of techniques to**
12 **make measurements, and sometimes the observations that**
13 **we make with those techniques are caused by limitations**
14 **of those techniques and don't reflect what we're trying**
15 **to actually measure. Those would be examples of**
16 **artifacts.**
17 Q. And so to the extent it's helpful to answer
18 your question, if you look at paragraph 7 of your
19 declaration, in the last two sentences you refer to
20 artifacts?
21 **A. I see that.**
22 Q. And your reference is to -- I'm looking at the

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1 last two sentences of paragraph 7:
2 "PCR can result in artifacts that
3 reduce the accuracy of nucleic acid
4 quantification and mutational analysis.
5 To mitigate these artifacts, I have
6 frequently developed an important library
7 construction and computational methods for
8 single-cell analysis that incorporate UMIs."
9 So when you use artifacts in these two
10 sentences, are you referring to the
11 observations that are caused by limitations in
12 the techniques you are using that don't reflect
13 what you're trying to actually measure?
14 **A. For example, the use of the term artifact in**
15 **the first sentence, where it says, "PCR can result in**
16 **artifacts that reduce the accuracy of nucleic acid**
17 **quantification," that's a direct reference to the type**
18 **of artifact that's illustrated in Figure 1A of the**
19 **Shiroguchi et al., paper.**
20 **So PCR can distort the relative abundance of**
21 **nucleic acids in a sample, and we use, as it states**
22 **here, library construction and computational methods**

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1 **that incorporate UMIs to mitigate those artifacts.**
2 Q. So after nucleic acid quantification, there is
3 end mutational analysis.
4 So the artifacts that you are referring to are
5 not limited to the distortion in the relative abundances
6 reflected in your paper, correct?
7 **A. PCR can also result in artifacts that impact**
8 **mutational analysis and library construction, and**
9 **computational methods that incorporate UMIs can also**
10 **serve to mitigate those types of artifacts.**
11 Q. So sitting here today, you can't give me a
12 definition of what you mean by artifacts?
13 MR. FLETCHER: Objection.
14 Q. You've given me examples, but can you give me a
15 definition?
16 MR. FLETCHER: Objection.
17 **A. The word "artifact" is extremely context**
18 **dependent, and so that's why I am limiting the way in**
19 **which I use it to these specific examples. I think I**
20 **have accurately described my perspective on the word**
21 **"artifact."**
22 Q. So if we look at your paper, in the second

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1 paragraph after the abstract, that sentence reads:
2 "The interpretation of conventional RNA
3 seq is complicated by sequence-dependent bias
4 and amplification noise from reverse
5 transcription adaptor ligation library
6 amplification by PCR solid-phase clonal
7 amplification and sequencing."
8 Do you see that?
9 **A. I see that.**
10 Q. And do you have an understanding as to what's
11 meant by "amplification noise" here?
12 **A. In this sentence we're drawing a contrast**
13 **between sequence-dependant bias and amplification noise**
14 **to distinguish two different situations, one in which**
15 **DNA polymerase acts with different efficiency on nucleic**
16 **acid fragments with different sequences and another in**
17 **which DNA polymerase stochastically amplifies nucleic**
18 **acids with the same sequence with different**
19 **efficiencies. The latter is referred to as**
20 **"amplification noise."**
21 Q. Can you explain what you mean by
22 "stochastically amplifies nucleic acids"?

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1 **A. By stochastic I mean random.**
2 Q. So a little bit further down in that same
3 paragraph -- I guess it's the second sentence from the
4 end -- the paper states "other methods."
5 Do you see the sentence starting --
6 **A. I see that.**
7 Q. "Other methods reduce bias in RNA seq by
8 eliminating PCR and directly sequencing single molecules
9 of RNA or sequencing single clonal populations of cDNA."
10 Do you see that?
11 **A. I see that.**
12 Q. So how do these methods reduce bias in the RNA
13 seq?
14 **A. PCR can distort the relative abundance of**
15 **nucleic acid fragments in a sample. These methods forgo**
16 **PCR. They sequence the molecules from the sample**
17 **directly.**
18 MS. CIPRIANO: Okay. I think I'm done
19 with this paper, and it might be a good time to
20 break for lunch.
21 MR. FLETCHER: Yes, lunch is ready.
22 Thank you.

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1 (Whereupon, a luncheon recess was taken
2 from 12:26 p.m. to 1:13 p.m.)
3 BY MS. CIPRIANO:
4 Q. Okay. Welcome back, Dr. Sims. Okay. You
5 still have your declarations in front of you, right?
6 **A. I do.**
7 Q. If you could turn to paragraph 84.
8 Are you there?
9 **A. I'm there.**
10 Q. And this -- you talk about the common
11 high-level process of next-generation platforms; is that
12 accurate?
13 **A. Yeah. This paragraph discusses some of the**
14 **common procedures used in next-generation sequencing**
15 **with multiple platforms.**
16 Q. Okay. So I'd like to walk through and talk
17 about each of these steps a little bit and get on the
18 same page with that -- what we mean. The first bullet
19 point under paragraph 84 is entitled "Library
20 Preparation."
21 What do you -- what does library preparation
22 mean to you?

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1 **A. Library preparation is a series of molecular**
2 **biology steps that makes nucleic acid fragments**
3 **compatible with, for example, next-generation**
4 **sequencing.**
5 Q. And in your experience, are there aspects of
6 the library preparation process that can cause errors in
7 the ultimate sequencing data that is gathered end of the
8 process?
9 (Reporter clarification.)
10 Q. Did you understand my question?
11 **A. Can you repeat the question?**
12 Q. Yes.
13 **A. Thank you.**
14 Q. Yes, we can --
15 **A. Sorry.**
16 Q. That's okay.
17 In your experience, are there aspects of the
18 library preparation process that can cause errors in the
19 ultimate sequencing data that is gathered at the end of
20 the next-generation sequencing process?
21 **A. Some library preparation methods include PCR,**
22 **and as we discussed earlier today, PCR can lead to the**

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1 **incorporation of substitution errors, for example, in**
2 **two nucleic acid fragments.**
3 Q. So earlier today we talked about a couple of
4 different aspects of PCR reactions that can lead to, in
5 the umbrella term of "error," in the ultimate library
6 preparation; is that accurate? What we talked about
7 earlier?
8 **A. Earlier we discussed some of the things that**
9 **can happen in a PCR reaction that can lead to, for**
10 **example, distortion of the relative abundance of nucleic**
11 **acids, the inclusion of errors like substitution errors.**
12 Q. Okay. So all of the problems of PCR have the
13 potential of impacting the ultimate data that is
14 gathered from next-generation sequencing processes,
15 right?
16 **A. Artifacts from PCR can impact the output of a**
17 **sequencing experiment like a next-generation sequencing**
18 **experiment.**
19 Q. Is PCR the only source of error in library
20 preparation that can impact the output of a sequencing
21 experiment?
22 **A. PCR is not the only step in library preparation**

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1 **that can impact the output of a sequencing experiment.**
2 Q. And what are the others steps that can impact
3 the output of a sequencing experiment?
4 **A. Some library preparation methods involve other**
5 **steps such as ligation. There are various ways in which**
6 **a ligation reaction can go wrong.**
7 Q. Are there any other examples of steps in the
8 library preparation process, then, that can introduce
9 errors?
10 **A. Some library preparation processes require**
11 **nucleic acid fragmentation. There are many methods for**
12 **fragmenting nucleic acids. There are things that can go**
13 **wrong during those processes as well.**
14 Q. Are there any others?
15 **A. There are probably others, but those are the**
16 **ones that come to mind.**
17 Q. Okay. So the next step -- the next bullet
18 point you have in paragraph 84 is "annealing to a
19 surface."
20 Can you explain what annealing to a surface
21 means in terms of the steps that go into a
22 next-generation platform?

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1 **A. In this context, the word "annealing" means**
2 **hybridization by Watson-Crick base pairing. And in this**
3 **section of my declaration, there are three**
4 **next-generation sequencing platforms referred to. All**
5 **three of those platforms use surfaces with**
6 **oligonucleotide primers attached to them.**
7 **So in this context, annealing to a surface**
8 **means that members of your nucleic acid fragment library**
9 **anneal, or hybridize, to the primers fixed to those**
10 **solid surfaces.**
11 Q. And you've listed three -- you mentioned that
12 you listed three of the next-generation platforms -- the
13 454, Illumina, and Ion Torrent.
14 Were those -- why do you list those three in
15 this section of your declaration?
16 **A. Those three platforms are used in some of the**
17 **references in my declaration -- some of the prior art**
18 **references, and so I thought it would be appropriate to**
19 **explain how they work.**
20 Q. Were those the three most popular
21 next-generation platforms in the 2011/2012 timeframe?
22 **A. It's fair to say that, by that time, Illumina**

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1 was significantly more widely used than the other two.
2 Q. Is the process of annealing the fragments to a
3 surface a source of error in the sequencing data that
4 that results from a next-generation sequencing process?
5 A. I wouldn't consider that step to be a major
6 source of error.
7 Q. Okay. The next step you talk about is
8 on-surface amplification. Can you explain what the
9 on-surface amplification step is referring to?
10 A. After annealing members of a nucleic acid
11 fragment library to a surface, these three platforms use
12 various methods of clonally amplifying those fragments
13 on the surface.
14 Q. What do you mean by clonally amplifying?
15 A. I'll use the 454 platform as an example,
16 because they all do it slightly differently.
17 So, for example, in the 454 platform, an
18 individual nucleic acid fragment molecule would anneal
19 to primers on the surface of a single bead. So you'll
20 typically have a situation where one bead has one
21 nucleic acid fragment bound to its surface and then a
22 PCR reaction takes place that results in the amplicons

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1 also being bound to that same surface.
2 Q. To the same bead?
3 A. The same bead.
4 Q. Okay.
5 A. And so the reason I use the word "clonal" is
6 because the amplicons originate from one molecule.
7 Q. Understood.
8 And so when PCR is used in this on-surface
9 amplification step, do all of the issues that we've
10 talked about with PCR generating errors, do they apply
11 equally to the onsite amplification step?
12 A. The types of errors that we discussed can
13 occur, but because of the clonal nature of the PCR, they
14 are far less likely to impact the sequencing results.
15 Q. And why are they far less likely to impact the
16 sequencing results?
17 A. I think it might help to give an example.
18 Q. Okay.
19 A. During a PCR reaction that's clonal, it's
20 possible that a subset of the molecules on the surface
21 might have an error in them because the DNA polymerase
22 makes a mistake. But that will typically be a minor

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1 fraction of the clonally amplified fragments that end up
2 on the surface. And so when you then sequence that
3 population of amplicons, the rare subset of them that
4 contain an error are very unlikely to distort the
5 sequencing results. This is part of the -- this is an
6 important part of the design of these platforms.
7 Q. And when you say "this" is important, the
8 clonal amplification? Is that what you're referring to?
9 A. The clonal amplification strategy is an
10 important part of the design of these platforms in part
11 because it greatly limits the impact of such errors.
12 Q. And since here, you're not dealing with a
13 mixture of nucleic acid fragments, the distortion of the
14 relative proportion of fragments is not an issue here
15 either, right?
16 A. I would not expect it to be a major problem
17 except in extreme cases.
18 Q. Okay. The next bullet point in this section of
19 your declaration is "Massively Parallel Sequencing."
20 Do you see that?
21 A. I see that.
22 Q. What do you mean by "massively parallel

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1 sequencing"?
2 A. What I mean by massively parallel sequencing is
3 that these three platforms are able to sequence many DNA
4 fragments in parallel; millions or even billions of
5 them.
6 Q. So this is the step where the sequence data is
7 collected by the -- by the platform; is that accurate?
8 A. We would refer to this step as the sequencing
9 step, but it's important to note that the form of the
10 data that results from this step can be somewhat removed
11 from actual sequences. For example, on the Illumina
12 platform, the sequencing process involves imaging.
13 Those images are then converted into sequencing
14 information --
15 Q. Okay.
16 A. -- by the computer.
17 Q. So this is -- when you refer to the "massively
18 parallel sequencing," it is, like several of the other
19 categories that you put in this, it's a sequence of
20 steps of data collection where you're converting the
21 sequencing library to data; is that fair?
22 A. The sequencing step takes that clonally

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1 **amplified nucleic acid fragment library and generates**
2 **sequencing data, but there are many components of that.**
3 Q. All right. In your experience is the
4 sequencing step of next-gen sequencing processes a
5 source of error in the ultimate sequencing data?
6 **A. All three of these platforms use DNA polymerase**
7 **as part of the sequencing process, and DNA polymerase**
8 **can make mistakes.**
9 **Also, all three of these platforms rely on**
10 **chemical steps happening in parallel on many clonal**
11 **copies of a given nucleic acid fragment, and**
12 **occasionally those steps get out of synch with each**
13 **other. That can cause errors.**
14 **There's also instrumentation associated with**
15 **these machines, imaging systems that have limitations,**
16 **so there are sources of errors.**
17 Q. And so the last step in this paragraph that you
18 have bulleted is computational processing in sequence
19 determination.
20 Can you explain what you mean by this step?
21 **A. So this process is platform-specific, but for**
22 **example, on the Illumina sequencing platform, this**

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1 **process would convert fluorescence imaging data into**
2 **nucleic acid sequence data using computer algorithms.**
3 Q. And is the computational process and sequence
4 determination a source of error in next-generation
5 sequencing processes?
6 **A. I don't want to imply that the computer is**
7 **going to make a mistake in executing an algorithm that**
8 **you give it, but the computer programs used for tasks**
9 **like base calling, are trying to compensate for some of**
10 **the errors that can occur during the sequencing process,**
11 **and they are imperfect.**
12 Q. Now, would you agree that reducing the amount
13 of error in any one step has the ability to improve the
14 quality of the ultimate sequencing that results from a
15 next-generation sequencing process?
16 **A. I think there are some steps where attempting**
17 **to mitigate errors would have a negligible impact on the**
18 **data for a lot of applications.**
19 Q. And what are those steps?
20 **A. As one example, trying to mitigate errors made**
21 **by the DNA polymerase during clonal amplification is**
22 **probably not going to have a huge impact on the quality**

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1 **of the sequencing data because of its clonal nature.**
2 Q. And so in your opinion, which sources of
3 error -- sorry. Let me rephrase.
4 In your opinion, which steps would be most
5 impactful to attempt to mitigate errors in a
6 next-generation sequencing process?
7 **A. This is very application-specific, but for**
8 **example, if one is trying to detect mutations on the**
9 **genome, then errors that induce artifactual mutations**
10 **are particularly problematic.**
11 Q. So, sorry, I don't think your answer exactly
12 answers my question.
13 You're giving one example when you're looking
14 for mutations; you want to avoid artifact mutations.
15 What step would you target in the
16 next-generation sequencing process to mitigate those
17 kinds of errors?
18 **A. Well, it sort of depends who you are. If**
19 **you're working at Illumina, you might try to improve the**
20 **sequencing instrumentation, and Illumina, for example,**
21 **has made improvements by changing the accuracy of the**
22 **sequencing instrumentation.**

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1 **If you're working in my lab, you might**
2 **implement steps in library preparation that could help.**
3 Q. So you'd agree that there are various ways to
4 improve on the ultimate sequencing data by impacting
5 various steps in the next-generation process --
6 next-generation sequencing process?
7 **A. The process as described in paragraph 84 of my**
8 **declaration have many steps, and there are multiple**
9 **opportunities to intervene and improve the quality of**
10 **sequencing data as a result.**
11 Q. And each individual improvement has a potential
12 to ultimately impact the sequencing data that's the
13 result of the next-generation process, right?
14 **A. As I mentioned before, I think there are some**
15 **steps where you are very unlikely to make substantial**
16 **improvements.**
17 Q. But there are some steps where you would expect
18 to see substantial improvements, correct?
19 **A. There are some steps where you are more likely**
20 **to improve the sequencing data in an**
21 **application-specific way.**
22 Q. And the two ways that you specifically

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1 mentioned that may have a significant impact would be a
2 library preparation step and potentially the sequencing
3 instrumentation steps. Is that accurate?
4 **A. Those are the two steps that I mentioned.**
5 Q. Are there other steps that you think would have
6 a significant impact if you improve the error rate?
7 **A. I wouldn't discount the possibility, but those**
8 **are two steps with which I am very familiar.**
9 Q. Okay. So in both of your declarations, you
10 have a section on -- that describes the work that is
11 done -- that was done at MGH. And this is in the
12 section of your declarations that are differently
13 numbered.
14 So in the declaration we've been looking at,
15 which is Exhibit 1079, I have that down as starting on
16 paragraph 176.
17 **A. Okay. I'm there.**
18 Q. And just for the record, in the other
19 declaration for the other proceedings in Exhibit 1085,
20 that starts at paragraph 112.
21 And from my read, the paragraphs are slightly
22 different but both of the sections have the same heading

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1 which is the MGH Archer Anchored Multiplex PCR Library
2 Preparation Method.
3 Are you there?
4 **A. I see that.**
5 Q. Okay. So here, you talk about work that was
6 done at Massachusetts General Hospital and published in
7 an article. And in your declaration that's marked 1085
8 for the '00015 and '00016 --
9 **A. Mm-hmm.**
10 Q. -- proceedings -- I'll give you a second to get
11 there.
12 In paragraph 113, you say:
13 "Prior to the publications of the Zheng
14 paper, I understand that MGH authors, the BMGH
15 authors filed for patents on their work."
16 Do you see that?
17 **A. I see that.**
18 Q. And that's including a patent application that
19 was filed as US Publication Number 2013/0303461, and
20 that's a -- I believe you pronounced it differently than
21 I have been pronouncing it in my head, but the Iafrate
22 reference that you talk about in your declarations; is

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1 that accurate?
2 **A. Yeah, this patent application is referred to in**
3 **my declaration. I've been pronouncing it Iafrate.**
4 Q. Okay.
5 **A. I don't know if I'm correct or not.**
6 Q. I'll try to get on the same page. That's been
7 stuck in my head for a while, so I don't know if I'll be
8 able to correct the habit.
9 So it's your understanding that the Iafrate
10 reference is a patent on the work that was done at MGH?
11 Patent application -- excuse me, that was done on the
12 work at MGH; is that accurate?
13 **A. That's consistent with my understanding.**
14 Q. Now, in paragraph 120 of your Exhibit 1085
15 declaration, you state your opinion that:
16 "A POSA would understand that the MGH
17 method is fundamentally different from the
18 method disclosed by NuGen in the '012 and '108
19 patents."
20 Do you see that?
21 **A. I'm sorry, which paragraph? We're in 1085?**
22 Q. Yeah. 120.

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1 **A. 120. Sorry.**
2 **I see that.**
3 Q. You'd also agree that the MGH method described
4 in the Iafrate -- is the way that it is in my head.
5 **A. That's fine.**
6 Q. I'm sorry.
7 You agree that the MGH described in the Iafrate
8 is different from the method disclosed in the '241, '357
9 and '399 patents, correct?
10 MR. FLETCHER: Objection.
11 **A. There are definitely differences in what is**
12 **disclosed in those patent applications.**
13 Q. Let's clarify that. There are definitely
14 differences between what's disclosed in Iafrate and the
15 '241, '357 and '399 patents; is that accurate?
16 **A. There are definitely differences in what's**
17 **disclosed in the '399, '357, '241 patents and what is**
18 **disclosed in the Iafrate application.**
19 Q. Sitting here now, and we'll go into this in
20 detail, but do you have examples in your mind of how
21 they are different?
22 **A. The '399, '357 and '241 patents are focused on**

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1 **methods for de-duplicating reads in sequencing data.**
2 **The Iafrate application is not focused on this.**
3 Q. Okay. So looking at your 1079 declaration,
4 Exhibit 1079, could we turn to paragraph 183?
5 **A. I'm there. I'm there.**
6 Q. And this is a section that's entitled, "A
7 Person of Ordinary Skill in the Art," I think we've
8 already been using the abbreviation, but you understand
9 that POSA is a shorthand for person of ordinary skill in
10 the art?
11 **A. I understand that.**
12 Q. And your declarations, you assumed a particular
13 level of expertise for this person of ordinary skill in
14 the art.
15 How did you arrive at the skill set you
16 supplied here?
17 **A. I discussed this topic with counsel and drew on**
18 **my experience training scientists in this field.**
19 Q. Do you understand that the PTAB panel disagreed
20 with portions of your definition of a person of ordinary
21 skill in the art?
22 **A. I have some recollection that they commented on**

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1 **my definition. I don't recall the details sitting here**
2 **right now.**
3 Q. I can show you the panel's decision, if it's
4 helpful, but if you were to apply the panel's definition
5 that it set forth, if you recall it, would it change
6 your positions in your declaration?
7 **A. I don't recall the panel's comments on the**
8 **definition of a POSA as the type of thing that would**
9 **impact the opinions set forth in my declaration.**
10 Q. Okay. If we can skip ahead to -- no, skip
11 back -- to backtrack in your declaration a little bit to
12 the prior art sections, and specifically I want to turn
13 to paragraph 129.
14 And just to orient you, feel free to look at
15 whatever you need to to answer my questions, but this is
16 a section that's talking about the McCloskey reference.
17 **A. I see that.**
18 Q. Now, the last sentence of paragraph 129 --
19 yeah, the last sentence of paragraph 129 says:
20 "Along with continuing to improve on
21 the use of molecular tags incorporated into
22 adaptors, scientists in the field also started

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1 to explore using the sequence of the nucleic
2 acid fragment from the sample as a unique
3 identifier or an endogenous molecular tag."
4 Do you see that?
5 **A. I see that.**
6 Q. There's no citation to this sentence. Do you
7 recall where -- what you were referring to when you said
8 this?
9 **A. As someone working in this field in 2010, this**
10 **sentence reflects my perspective on how the field was**
11 **evolving. However, in my declaration, I do discuss**
12 **specific examples of these technologies.**
13 Q. And what you're talking about is where it says,
14 for example, in paragraph 130 and later? Is that what
15 the examples you're referring to?
16 **A. Those are some of the examples.**
17 Q. Okay. You're not saying that McCloskey
18 disclosed that concept, right?
19 **A. Which concept?**
20 Q. The use of -- the sequence of the nucleic acid
21 fragment from the sample as a unique identifier or an
22 endogenous molecular tag?

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1 **A. Sitting here today, I don't recall whether**
2 **McCloskey used, for example, features -- sequence**
3 **features of the nucleic acid fragment as part of the**
4 **unique identifier.**
5 Q. Okay. If we could -- I'd like to talk about
6 another reference you talk about, referred to as
7 Schmidt, which is at paragraph 164 of your declaration.
8 **A. I'm there.**
9 Q. Do you recall the Schmidt reference, or would
10 you like to see it?
11 **A. Probably depends on your next question.**
12 Q. So you let me know. I have copies.
13 **A. I'll let you know.**
14 Q. Understood.
15 So if you look at paragraph 125, you have a
16 quote from Schmidt. And in that -- in, I guess, the
17 second part of the first sentence:
18 "After sequencing, members of each PCR
19 family are identified and grouped by virtue of
20 sharing an identical tag sequence."
21 **A. Sorry. You said paragraph 125?**
22 Q. I'm sorry. 165.

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1 **A. Okay.**
2 Q. I misspoke.
3 **A. Okay. Yeah, I see that.**
4 Q. And then you go onto explain that, after
5 grouping by tags, the sequences were compared to create
6 a consensus sequence.
7 Do you see that? There's another quote from
8 Schmidt further down in that paragraph.
9 **A. I see that.**
10 Q. What is a consensus sequence in your
11 understanding?
12 **A. A consensus sequence is a sequence that one**
13 **arrives at by analyzing multiple reads and then making a**
14 **judgment as to what the correct sequence of the**
15 **originating nucleic acid fragments likely is.**
16 Q. So in Schmidt, it was a two-step process to
17 arrive at the consensus sequence. First they grouped
18 the reads into -- by virtue of their identical tag
19 sequences, and then they generated the consensus
20 sequence; is that right?
21 **A. I agree that there are multiple steps involved**
22 **in the process described by Schmidt, but I would**

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1 **probably need to see the reference to fully refresh my**
2 **memory on the details.**
3 Q. Okay. I don't think that -- I think that's
4 helpful enough. Thank you.
5 Okay. I'd like to next talk about the Kivioja
6 reference. And that's again, how it's stuck in my head,
7 but I know that -- I believe you pronounced it
8 differently. We can look at -- to the extent you want
9 to look at your declaration, we can look here starting
10 paragraph 248, I think, I have in my notes?
11 **A. I'm there.**
12 Q. It starts before that but understood.
13 So in your declaration, you have made arguments
14 that the asserted claims -- the challenged claims,
15 excuse me -- of the '241, '357 and '399 patents are
16 obvious in light of a combination of Kivioja and
17 Iafrate; is that right?
18 **A. My opinion is that claims of the '399, '357 and**
19 **'241 patents are obvious given the combination of**
20 **Iafrate and Kivioja.**
21 Q. So I'd like to focus on limitation 1D, what
22 we've -- what your declaration identifies as limitation

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1 1D of -- this is of the '399 patent in paragraph 248.
2 And it's your opinion that Kivioja discloses
3 this limitation, which is limitation 1D -- sorry. I'm
4 going to start over anyway because I'm -- thank you.
5 So what's been defined as limitation 1D is the
6 limitation that recites:
7
8 "Identifying a duplicate sequencing
9 read comprising the same identifier site and
10 nucleic acid fragment as another sequencing
11 read in a population of sequence reads."
12 Is that right?
13 **A. I see that's the text of Claim 1D.**
14 Q. And that's of the '399 patent as it's cited in
15 paragraph 248 of your declaration?
16 **A. Yes. That's the '399 patent, yeah.**
17 Q. And for this limitation in part of 248, you
18 pointed to the quote in Kivioja that reads -- and this
19 is a couple of lines down:
20 "The mapped reads with the same gene,
21 position, and label were collected to one UMI,
22 and the number of such reads was recorded as

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1 the copy number of that UMI."
2 Do you see that?
3 **A. I see that.**
4 Q. Now, the challenge claims don't use the term
5 "UMI," right?
6 **A. The challenge claims do not use that term.**
7 Q. The challenge claims require a comparison of an
8 identifier site and a nucleic acid fragment.
9 Is that your understanding of the terminology?
10 MR. FLETCHER: Objection.
11 **A. I see that Claim 1D uses the terms "identifier**
12 **site" and "nucleic acid fragment."**
13 Q. And am I correct that you interpret the label
14 in Kivioja to be what is referred to as an identifier
15 site of the '399 patent?
16 **A. So as stated in my declaration, in paragraph**
17 **276, the last sentence:**
18 **"Kivioja discloses identifying a**
19 **duplicate sequencing read as a sequencing read**
20 **comprising the same identifier site," and then**
21 **in parentheses, "the label." And then it goes**
22 **on.**

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1 **So that's where I'm drawing the**
2 **equivalence between the identifier site and the**
3 **label.**
4 Q. And in that same sentence, you equate nucleic
5 acid fragment, which is a term used in the claim, with
6 the gene and position referred to in Kivioja, right?
7 **A. The gene and position is a way in which Kivioja**
8 **encodes the nucleic acid fragment information.**
9 Q. What do you mean by "encodes"?
10 **A. Kivioja sequences nucleic acid fragments and,**
11 **among other things, records their gene and position.**
12 **And that information is part of the unique molecular**
13 **identifier that Kivioja uses for de-duplicating**
14 **sequencing reads.**
15 Q. You agree that the nucleic acid sequence and
16 the gene that that sequence is a part of are different
17 types of information?
18 MR. FLETCHER: Objection.
19 **A. When one sequences a nucleic acid fragment,**
20 **that sequence -- that observed sequence can differ from**
21 **the sequence on the genome from which that nucleic acid**
22 **fragment originated.**

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1 Q. That's not quite my question.
2 **A. Okay.**
3 Q. So when we are talking about the nucleic acid
4 sequence, that's going to be the data that is the order
5 of As, Ts, Gs and Cs.
6 Is that your understanding?
7 **A. I think the subtlety here is that, in a**
8 **sequencing experiment, one has an observed sequence for**
9 **a given read corresponding to a nucleic acid fragment,**
10 **and one may also have a reference sequence that's known**
11 **a priori. I'm sort of pointing out that those can be**
12 **different from each other.**
13 Q. Okay. But that's -- so my question is simply
14 that when we're talking about a nucleic acid sequence,
15 we are talking about a series of letters, and that's the
16 data that is the sequence, correct?
17 **A. A nucleic acid sequence can be described as a**
18 **series of letters.**
19 Q. And when -- when you take the other step and
20 map it to a known genome, when you identify a sequence
21 as part of a gene, then you're identifying how ever the
22 gene is named; is that accurate?

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1 **A. When you align a sequencing read to a genome,**
2 **you get multiple pieces of information including the**
3 **name of the gene to which it aligns, the position within**
4 **the gene and within the genome to which it aligns, and**
5 **you can also get an assessment of how that sequencing**
6 **read differs from the reference genome.**
7 Q. So the information that Kivioja uses as part of
8 its -- what it calls its UMI are the first two pieces of
9 information on your list -- the name of the gene and the
10 fragment's position in that gene, right?
11 **A. Kivioja uses the name of the gene and the**
12 **position to -- the position within that gene to which**
13 **the sequencing read aligned.**
14 Q. So in order to do the -- to create the UMIs
15 that Kivioja used and talked about in its -- in that
16 paper -- sorry. Let me pause there.
17 Okay. So let's look at paragraph 248 of your
18 declaration.
19 **A. I'm there.**
20 Q. So the -- I'm looking at the sentence that
21 spans pages 137 and 138 that reads:
22 "Specifically, for each gene, Kivioja

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1 mapped the sequencing read against the longest
2 transcript of that gene which was used as the
3 reference sequence."
4 Do you see that?
5 **A. I see that.**
6 Q. So Kivioja's first step is to take the sequence
7 data and compare it to a reference sequence; is that
8 accurate?
9 **A. Kivioja used a reference containing many**
10 **transcript sequences and performed an alignment against**
11 **that reference for each sequencing read in the data to**
12 **determine where each sequencing read aligned to the**
13 **extent that that read aligns anywhere.**
14 Q. So let's look at the actual reference of
15 Kivioja. We're going to look at Exhibit 1012. I'd like
16 to look at -- well, first of all, you recognize Exhibit
17 1012, right?
18 **A. I recognize Exhibit 1012.**
19 Q. And it's the Kivioja reference that you cite to
20 in your declaration?
21 **A. This is the Kivioja reference that I cite in my**
22 **declaration.**

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1 Q. And I'd like you to turn to -- it's the page --
2 it's part of the "Online Methods" section. It's the
3 page that's marked at the bottom as Exhibit 1012.0004?
4 **A. I'm there.**
5 Q. Okay. At the bottom of the first paragraph of
6 the "Digital Karyotyping" section -- it's in the
7 left-hand column of that page -- in the last sentence,
8 it says:
9 "Sequences were generated on an
10 Illumina Genome Analyzer with 76 bp single
11 reads for the mixed sample and 100 bp
12 paired-end reads for the adult male sample.
13 Reads were mapped to the genome using Bowtie."
14 Do you see that?
15 **A. I see that.**
16 Q. Do you know what is referenced as Bowtie here?
17 **A. Bowtie is a computer program which, among other**
18 **things, can align or map sequencing reads to a reference**
19 **set of sequencing reads such as a reference genome.**
20 Q. So if we look at the next page in the section
21 that's -- has the heading "mRNA SEQ Data Analysis"?
22 **A. I see that.**

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1 Q. You see that? Okay. In the second paragraph
2 of that section, it says:
3 "For each gene, the sequence of its
4 longest transcript was used as the reference
5 sequence."
6 Do you have an understanding of what is
7 being referred to as the reference sequence
8 here?
9 **A. So the sample under study in this section of**
10 **the paper is from Drosophila, and some genes in the**
11 **Drosophila genome have multiple isoforms. Kivioja**
12 **selected the longest isoform in terms of number of**
13 **nucleotides for each gene and used that as the reference**
14 **sequence for that gene.**
15 Q. So when it talks about the longest transcript,
16 it's not talking about the longest transcript detected
17 in the Kivioja sequence, right? This is a pre-published
18 or known sequence of the Drosophila genome; is that
19 accurate?
20 **A. This is in reference to a pre-published**
21 **reference for the Drosophila transcriptome.**
22 Q. So in that same paragraph we were just talking

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1 about with the reference sequence sentence, there's an
2 explanation of some data analysis where reads were
3 discarded for certain -- under certain circumstances.
4 Do you see that?
5 **A. I see that.**
6 Q. This section of data analysis, that happened
7 after the reads were mapped to the genome using Bowtie;
8 is that accurate?
9 MR. FLETCHER: Objection.
10 **A. Bowtie was not used for alignment in this**
11 **section of the paper. Instead a different piece of**
12 **software called the Burrows-Wheeler Aligner was used.**
13 Q. I understand.
14 **A. However, these steps likely occurred after**
15 **alignment. Some of these steps require information from**
16 **the aligner.**
17 Q. So then in the next paragraph, in that same
18 section, in the first sentence of that third paragraph
19 reads:
20 "The mapped reads that the same gene
21 position and label were collected to one UMI
22 and the number of such reads was recorded as

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1 the copy number of that UMI."
2 Do you see that?
3 **A. I see that.**
4 Q. And that's the -- that's the sentence that you
5 quote in your declaration as supporting your position
6 that Kivioja discloses the limitation 1D of the
7 challenge claims; is that accurate?
8 I can point you to paragraph 248, if that's
9 helpful.
10 **A. Yeah. I quote that sentence in reference to my**
11 **opinion that Kivioja discloses the limitation in Claim**
12 **1D.**
13 Q. Okay. And that analysis where Kivioja collects
14 mapped reads to UMI, that's -- we have talked about the
15 third step of data analysis after sequencing at least,
16 right?
17 MR. FLETCHER: Objection.
18 **A. We've discussed alignment as a first step, a**
19 **second multistep process where reads are discarded based**
20 **on certain criteria and then the third step, which is**
21 **described in that sentence that you read.**
22 Q. So after the reads are collected to their UMIs

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1 in Kivioja, the process there is that Kivioja counts the
2 reads, right?
3 And I can point you to paragraph 239, to the
4 extent it's helpful.
5 **A. Kivioja describes a process by which UMIs are**
6 **established from the data and then those UMIs are used**
7 **for quantifying or counting the number of molecules**
8 **corresponding to a given nucleic acid fragment in the**
9 **original sample.**
10 Q. You describe this in paragraph 239 of your
11 declaration as "collapsing."
12 Do you see that?
13 **A. I see the sentence where I used the term**
14 **"collapsed."**
15 Q. But is collapsing data the same as removing
16 data, in your opinion?
17 **A. Some sequence information is removed in this**
18 **collapsing process.**
19 Q. In what way is it removed?
20 **A. For example, if a pair of reads each have the**
21 **same label or molecular tag and the same nucleic acid**
22 **fragment sequence, one of them might be removed in the**

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1 **collapsing process.**
2 **So you would -- you would have two reads, but**
3 **you would only count them as one.**
4 Q. Right. Is only counting them as one the same
5 as removing a duplicate?
6 MR. FLETCHER: Objection.
7 **A. The process I just described is often referred**
8 **to as de-duplication, so that could be construed as**
9 **removing duplicates or removing a duplicate.**
10 Q. Does Kivioja refer to de-duplication?
11 **A. I don't believe that Kivioja uses the term**
12 **"de-duplication," but it is a widely used term in**
13 **next-generation sequencing.**
14 Q. And for the counting method that you're relying
15 on for this process in Kivioja, that's depicted in
16 Figure 1A of the reference of Exhibit 1012; is that
17 right?
18 **A. Figure 1A is one illustration of the counting**
19 **method in Kivioja.**
20 Q. Is there another illustration of the counting
21 method in Kivioja?
22 **A. Figure 1B is also an illustration of the**

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1 **counting method in Kivioja.**
2 MR. FLETCHER: We've been going about
3 an hour and a half, let's take a break.
4 MS. CIPRIANO: Okay, let me finish this
5 reference. I have two questions on this
6 article.
7 MR. FLETCHER: Okay.
8 MS. CIPRIANO: And you know what, we
9 can -- yeah, we can move on, so let's take a
10 break.
11 (Whereupon, a short break was taken.)
12 BY MS. CIPRIANO:
13 Q. Okay. We can dive back in. So I'm going to
14 switch gears and talk a little bit about the Iafrate, is
15 that --
16 **A. Yep, that's how we're saying it, but, yeah.**
17 Q. Iafrate reference.
18 **A. Okay.**
19 Q. So if we can look in your declaration, we'll
20 start there, at paragraph 211.
21 **A. I'm there.**
22 Q. In the second half of paragraph 211, on this

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1 page, you walk through the adaptor that's identified in
2 Iafrate.
3 Do you see that?
4 **A. I see that.**
5 Q. And so you agree that the Iafrate adaptor does
6 not disclose the use of an identifier as part of this
7 adaptor, correct?
8 **A. The Iafrate adaptor does not include an**
9 **identifier or molecular tag as typically employed for**
10 **PCR de-duplication, for example.**
11 Q. And what do you mean by "typically" in that
12 sentence?
13 **A. I just mean that molecular tags are commonly**
14 **used for PCR de-duplication.**
15 Q. Okay. But the Iafrate adaptor does not include
16 a molecular tag or identifier site, right?
17 **A. The Iafrate adaptor does not include a**
18 **molecular tag or identifier site.**
19 Q. Okay. Let's flip to paragraph 454 of your
20 declaration. This is the beginning of the section where
21 you talk about your arguments related to the reference
22 that we've been referring to as Bielas, correct?

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1 **A. This is the section about the Bielas reference.**
2 **We've been saying Bielas.**
3 Q. Okay. So for -- just to make sure that we are
4 speaking the same language and that we are -- I don't
5 have to ask you the same question over and over again,
6 in this section, the section titles include the '399
7 patent, '357 patent and the '241 patents, right?
8 **A. I see that.**
9 Q. And you have a section that is, the section
10 starting at paragraph 456 is not patent-specific in your
11 discussion of the Bielas disclosures; is that an
12 accurate representation?
13 **A. This paragraph is a general discussion of the**
14 **Bielas disclosure that is related to all three of the**
15 **challenged patents.**
16 Q. Okay. And then starting at paragraph 487.
17 **A. I'm there.**
18 Q. At 487, you have a section that starts to talk
19 about the '399 patent specifically, right?
20 **A. This paragraph is about the '399 patent,**
21 **specifically. There may be some aspects that are**
22 **related to the other two, but the paragraph is focused**

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1 **on the '399 patent.**
2 Q. Okay. So I'd just like to make sure we're on
3 the same page. So the section starting at the top of
4 page 244 focuses on the '399 patent, and then in the
5 next -- in the following pages, you have an analysis of
6 Claim 1 of the '399 patent, and that extends through the
7 bottom of page 255 if -- if you could confirm that
8 that's your understanding as well?
9 **A. Those pages are focused on Claim 1 of the '399**
10 **patent.**
11 Q. And specifically anticipation of Claim 1,
12 correct?
13 **A. Those pages compromise section A entitled**
14 **"Bielas Anticipates Claim 1."**
15 Q. Okay. And then you have a couple of pages
16 devoted to the obviousness. Your position is that Claim
17 1 of the '399 patent is obvious based on Bielas, and
18 that's spanning pages 256 through the top of 260?
19 **A. 260 discusses how Claim 1 would have been**
20 **obvious based on Bielas.**
21 Q. Okay. And then following that section, there's
22 a discussion of the dependent claims of the '399 patent

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1 which extends through page -- midway through page 275.
2 Do you see that?
3 **A. I see that.**
4 Q. Okay. Then the remaining sections, so section
5 3 on page 275 starts talking about the '357 patent.
6 Do you see that?
7 **A. I see that.**
8 Q. And then in many of these sections, it refers
9 back to the discussion of the '399 patent.
10 Does that -- do you recall that?
11 **A. I recall that.**
12 Q. Okay. Now, can we agree that if we -- if I ask
13 you about a paragraph specifically related to the '399
14 patent and that paragraph is also referenced in the '357
15 patent or the '241 patent, that your testimony would
16 apply to the testimony -- the information that you
17 cross-referenced between the patents?
18 **A. Can you repeat that question?**
19 Q. Sure.
20 So we can look at an example. So for example,
21 on page 280 --
22 **A. Okay.**

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1 Q. -- there's a section for -- that's referring to
2 the element an identifying sequence reads with identical
3 identifier and target sequence as duplicates, right?
4 **A. I see that.**
5 Q. And here, you have a comparison of the language
6 of the '357 patent and the '399 patent, right, in the
7 chart?
8 **A. I see that.**
9 Q. And then you go through in paragraph 578, the
10 differences between the '357 and the '399?
11 **A. I see that.**
12 Q. Right?
13 And then in paragraph 579, you say:
14 "Because the identification step of the
15 '357 patent is also present in the '399 patent,
16 Bielas discloses this limitation for the
17 reasons state in section 6D.2.A.5 of my
18 declaration."
19 Do you see that?
20 **A. I see that.**
21 Q. So if I ask you questions about section 6D.2.A5
22 of your declaration, is it fair to also say that that

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1 testimony would apply to this element of the '357
2 patent?
3 **A. My testimony on section VI.D.2.A5 of my**
4 **declaration would apply to the identification step in**
5 **both the '357 patent and the '399 patent.**
6 Q. Okay. So thanks for being patient and walking
7 through that level setting with me.
8 If we could go back to the beginning of the
9 Bielas discussion and look at paragraph 459.
10 And in -- in paragraph 459, let's just get on
11 the same page. It reads:
12 "Thus, Bielas teaches a method of using
13 random molecular tags to identify PCR
14 duplicates of original molecules and then
15 de-duplicate those PCR copies in order to
16 determine, for example, whether a particular
17 mutation is present in the original fragment (a
18 true mutation) or was created during PCR
19 amplification (an artifact mutation)."
20 Do you see that?
21 **A. I see that.**
22 Q. Okay. So the purpose of identifying duplicates

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1 in Bielas was to determine if a mutation was an artifact
2 of PCR or a true mutation in the sample; is that
3 accurate?
4 **A. That is one application of the technology**
5 **disclosed in Bielas.**
6 Q. But that's how Bielas uses it, right?
7 **A. Bielas focused on that application.**
8 Q. So let's look at paragraph 508.
9 Are you there?
10 **A. I'm there, yes. Sorry.**
11 Q. And this -- again, this is in the section where
12 you are doing an element-by-element analysis of Claim 1
13 of the '399 patent, correct?
14 **A. That's correct.**
15 Q. And this is focusing on the element 1D, which
16 is identifying a duplicate sequencing read as a
17 sequencing read comprising the same identifier sites and
18 nucleic acid fragment as another sequencing read in the
19 population of sequencing reads, right? That's the
20 element we're talking about?
21 **A. I agree.**
22 Q. And in the second sentence of this paragraph,

123

1 after the introductory clause, you state:
2 "Bielas identified duplicate sequencing reads
3 using the sequence of a cypher and the sequence of a DNA
4 sequencing fragment in both Example 1 and Example 3,"
5 correct?
6 **A. I see that.**
7 Q. And do you rely on any other portions of Bielas
8 for this disclosure, or is it just examples 1 and 3?
9 MR. FLETCHER: Objection.
10 **A. There are other relevant sections of Bielas.**
11 **There are sections where certain terms that are used in**
12 **examples 1 and 3 are defined. Examples 1 and 3 refer to**
13 **figures. So it's multiple components taken together**
14 **with those two examples that I examined to form this**
15 **opinion.**
16 Q. Okay. So I'd like to take a look at the text
17 of Example 1 and Example 3. And this is -- we're going
18 to hand you Exhibit 1013, which was already marked as
19 the Bielas reference.
20 So, first of all, the exhibit I handed you
21 that's previously marked as Exhibit 1013, do you
22 recognize this document?

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1 **A. I recognize this document.**
2 Q. And this is the Bielas reference that you refer
3 to in your declaration?
4 **A. This is the Bielas reference.**
5 Q. So let's turn to page 24, which is the
6 beginning of the text of Example 1.
7 **A. I'm there.**
8 Q. Now, in your declaration -- and we can refer
9 back and forth if it's handy -- in paragraph 508, you
10 quote a section from the last paragraph of Example 1.
11 It's that first -- a portion of that first sentence of
12 the last paragraph of Example 1 which reads:
13 "The unique cypher tags are used to
14 computationally deconvolute the sequencing data
15 and map all sequence reads to single molecules
16 (i.e., distinguish PCR and sequencing errors
17 and from real mutations)."
18 Do you see that?
19 **A. I see that.**
20 Q. Do you understand what is meant by
21 "computationally deconvolute" in this sentence?
22 **A. My understanding of the term "computationally**

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1 **deconvolute" in Bielas is that Bielas used computer**
2 **programs to de-duplicate sequencing reads.**
3 Q. And what -- how are you making the connection
4 between deconvolute and de-duplicate?
5 **A. Aside from the broader context of the**
6 **disclosure in Bielas, a key phrase is "map all sequence**
7 **reads to single molecules."**
8 **So you have -- you can have multiple sequence**
9 **reads that are then considered to be single molecules or**
10 **to have originated from single molecules following the**
11 **deconvolution procedure.**
12 Q. So here, the sentence -- the "map all sequence
13 reads" is separate from computationally deconvolute,
14 right? The sentence reads:
15 "The cypher tags are used to, one" --
16 I'm adding that -- "computationally deconvolute
17 the sequencing data" and two, "map all sequence
18 reads."
19 What leads you to believe that they are
20 one and the same?
21 MR. FLETCHER: Objection.
22 **A. My interpretation of the sentence is that**

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1 **Bielas used a word "deconvolute," which has a broad**
2 **range of context-specific meanings, and then clarified**
3 **its meaning in this context with that second phrase,**
4 **"map all sequencing reads to single molecules."**
5 Q. Deconvolute can mean something other than
6 de-duplication, right?
7 **A. The word "deconvolute" can be used in different**
8 **ways in different contexts in different applications.**
9 **My interpretation is that, in this context, deconvolute**
10 **refers to the de-duplication process described in**
11 **Bielas.**
12 Q. Bielas doesn't call it de-duplication, right?
13 **A. I don't believe Bielas uses the term**
14 **"de-duplication."**
15 Q. Now, based on this sentence in Example 1,
16 Bielas states that the cypher tags were used to
17 deconvolute and map all sequence reads to single
18 molecules.
19 Bielas doesn't mention using the -- any
20 sequence information; is that accurate?
21 MR. FLETCHER: Objection.
22 **A. The cypher tags are sequence information.**

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1 Q. Let me clarify. Good point.
2 So Bielas explains that the cypher tags were
3 used to deconvolute and map sequences to single
4 molecules but doesn't refer to using any part of the
5 sequence of the target sequence in this process, right?
6 MR. FLETCHER: Objection.
7 **A. My interpretation of Bielas is that both the**
8 **sequence of the molecular tag or cypher and the sequence**
9 **of the DNA fragment are used in the de-duplication**
10 **process.**
11 Q. And what in Example 1 leads you to that
12 conclusion?
13 **A. There are multiple things in Example 1 in**
14 **addition to the broader context of the disclosure which**
15 **has a lot more information than is just in this**
16 **paragraph, but specific to this paragraph, there are a**
17 **few things.**
18 **One, that same sentence that we're reading**
19 **refers to real mutations. Real mutations cannot be**
20 **assessed without comparing the sequence of the DNA**
21 **fragment to, for example, a reference.**
22 **Another aspect of this paragraph is the second**

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1 **sentence. In the second sentence, Bielas mentions**
2 **sequence alignment. So this is presumably an assessment**
3 **of the target sequence with respect to a reference**
4 **genome.**
5 Q. What you're talking about in that second
6 sentence, that's done as a separate step from mapping
7 the sequence to single molecules, right?
8 MR. FLETCHER: Objection.
9 **A. Sequence alignment is a separate step.**
10 Q. Okay. So you also point to Example 3 in Bielas
11 that starts on paragraph 26 -- not paragraph, page 26 of
12 the reference.
13 **A. I see that.**
14 Q. And I believe in your declaration you
15 specifically quote from the results section of Example
16 3, and that starts on page 29.
17 **A. Sorry. Yes, I'm there.**
18 Q. Okay. And in that first sentence, the second
19 half, it says:
20 "All sequencing reads with identical
21 cypher pairs and their reverse complements were
22 grouped into families to create a consensus

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1 sequence."
2 Do you see that?
3 **A. I'm sorry. Can you tell me which line number**
4 **we're --**
5 Q. Yeah. It's the second half of that first
6 sentence. So it's line 27, the second half of line 27.
7 **A. Okay. Yes, I see that.**
8 Q. And we talked about the concept of a consensus
9 sequence earlier today, right?
10 **A. I recall discussing that.**
11 Q. Okay. Now, here it says -- this grouping into
12 families, that was based on the cypher pairs and their
13 reverse complements, right?
14 **A. The cypher pairs and their reverse complements**
15 **are used to group sequencing reads into families.**
16 Q. And based on this disclosure, nothing else was
17 used to create these families, correct?
18 **A. My interpretation of Example 3 is similar to my**
19 **interpretation of Example 1, which is that the cypher**
20 **sequence and the sequence of the DNA fragment are used**
21 **to identify duplicate sequencing reads and to collapse**
22 **those into single molecules.**

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1 Q. And what in Example 3 allows you to make that
2 conclusion?
3 **A. My conclusion is based, in part, on Figure 3B**
4 **which is referenced in Example 3 to illustrate the**
5 **process used by Bielas.**
6 Q. So Figure 3B, it's on the first page of the
7 exhibit. It's also in a bigger form on page -- the
8 easiest is at the bottom of the page. It's 1013.0043.
9 **A. I see that.**
10 Q. And here you have Cypher Family 1. And that
11 has a striped -- the batches on the ends of the lines
12 are the cyphers; is that accurate?
13 **A. Cypher Family 1 has vertical stripes and a dark**
14 **black rectangle that denote the cyphers.**
15 Q. Okay. And so Cypher Family 1, those all have
16 the vertical stripes on one end and a solid black
17 rectangle on the other end, correct?
18 **A. I see that.**
19 Q. And they have different dots in the -- in the
20 lines connecting the cyphers, which is, I think,
21 supposed to represent the sequence, correct?
22 **A. The little circles are representing certain**

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1 **nucleotide identities in the DNA fragment.**
2 (Reporter clarification.)
3 **A. I'm sorry. Nucleic acid fragment I think is**
4 **what I said. I think.**
5 Q. So the members of Cypher Family 1 do not all
6 contain the same nucleic acid sequence, correct?
7 **A. The sequencing reads in Cypher Family 1 do not**
8 **all have the same sequence.**
9 Q. They do, though, all have the same two cyphers,
10 right?
11 **A. They all have the same two cypher sequences.**
12 Q. So if we turn back to the paragraph at the
13 bottom of page 29 of Bielas?
14 **A. I see that.**
15 Q. Sorry. If we turn back to the bottom of page
16 29, I'd like to go through the steps that are outlined
17 in the results section. So in the top of that section:
18 "TP53 Exon 4 DNA from a dual cypher
19 vector library produced in E. Coli was
20 sequenced with a depth of over a million."
21 So that's the -- the samples were
22 sequenced, to put it in laymen's terms?

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1 **A. The samples were sequenced.**
2 Q. Okay. Then:
3 "All sequencing reads with identical
4 cypher pairs and their reverse complements were
5 grouped into families to create a consensus
6 sequence."
7 So that's what we were talking about
8 that's represented in Figure 3B, right?
9 **A. Figure 3B is describing this process.**
10 Q. Okay. So then -- then it goes on to say:
11 "As illustrated in Figure 3B, errors
12 introduced during library preparation (open
13 circle) and during sequencing (gray circle and
14 triangle) were computationally eliminated from
15 the consensus sequence, and only mutations
16 present in all reads (black diamonds, Figure
17 3B) of a cypher family were counted as true
18 mutations (see bottom of Figure 3B)."
19 Do you see that?
20 **A. I see that.**
21 Q. So Bielas decided whether to eliminate reads
22 based on the frequency of new mutations; is that

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1 accurate?
2 MR. FLETCHER: Objection.
3 **A. There are several things going on in the**
4 **analysis performed by Bielas. Bielas is removing**
5 **certain reads that contain single-nucleotide differences**
6 **that occur at lower frequencies than in other reads.**
7 **Bielas is also comparing the sequences of different**
8 **strands of the same originating molecule. Bielas is**
9 **also, in Figure 3B, annotating a specific nucleotide as**
10 **a "true mutation," which necessitates comparison to a**
11 **reference genome.**
12 **That is part of why I interpret Bielas as using**
13 **both information in the DNA fragment and the cypher in**
14 **this process.**
15 Q. Okay. Let's go back to my question.
16 Bielas -- when looking at the mutations in the
17 sequencing reads, Bielas eliminated unique mutations; is
18 that accurate?
19 MR. FLETCHER: Objection.
20 **A. There is an example in Figure 3B of a mutation**
21 **that occurs in only one fragment that was removed and**
22 **does not appear in the de-duplicated fragment. That**

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1 **would be, for example, the white triangle.**
2 Q. And so when Bielas is talking about
3 eliminating -- computationally eliminating -- from the
4 consensus sequence --
5 (Reporter clarification.)
6 MS. CIPRIANO: Consensus sequence.
7 (Reporter clarification.)
8 MS. CIPRIANO: I don't remember what I
9 said. Let me start over then.
10 BY MS. CIPRIANO:
11 Q. So Bielas is talking about computationally
12 eliminating data from the consensus sequence. And the
13 data that he's excluding in that process are errors
14 introduced during library preparation and errors
15 introduced during sequencing.
16 Is that a fair read of the information at the
17 bottom of page 29?
18 MR. FLETCHER: Objection.
19 **A. The Bielas technology is designed to remove**
20 **mutations that occur due to errors made by DNA**
21 **polymerase during PCR amplification and errors made**
22 **during sequencing.**

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1 Q. And when those errors are removed, they're not
2 looking for duplicates, right? They're looking for
3 errors?
4 MR. FLETCHER: Objection.
5 **A. Errors can arise in the form of PCR duplicates.**
6 **So for example, in Figure 3B, the nucleic acid fragment**
7 **with the triangle mutation is a PCR duplicate of the**
8 **other DNA fragments that are depicted there.**
9 **They originate from the same original -- sorry,**
10 **they originate from the same fragment in the original**
11 **sample.**
12 Q. But you would agree that the -- the nucleic
13 acid with the triangle mutation or indication in Figure
14 3B, that does not have a duplicate that is depicted in
15 Figure 3B, correct?
16 **A. My understanding of Figure 3B is that all of**
17 **the nucleic acid fragments depicted there are PCR**
18 **amplicons that came from the same original fragment.**
19 **They are all duplicates of each other.**
20 **I just will add one point of clarification. I**
21 **think of -- and I think the field broadly thinks of PCR**
22 **as a duplication process and what's shown in Figure 3B**

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1 **is a de-duplication process.**
2 Q. So if these are all duplicates in your
3 definition, how does Bielas distinguish between "real
4 mutations" and "error mutations"?
5 **A. The most basic criterion for identifying a real**
6 **mutation is that a nucleotide position must differ from**
7 **some reference.**
8 **Secondarily, Bielas is also assessing the**
9 **frequency with which a given nucleotide substitution**
10 **occurs among a group of reads.**
11 **And also, Bielas is comparing strands that**
12 **originate from the same original fragment and therefore**
13 **should have the same sequence.**
14 Q. So in Example 3 on page 30, looking at the
15 second paragraph for the results section, it says:
16 "Wild type TP53 exon 4 sequence was
17 compared to the actual sequence results and
18 substitutions were plotted."
19 Can you explain to me the difference
20 between the exon -- the wild exon 4 sequence
21 and the actual sequence results?
22 **A. In this context, the sequence of wild type TP53**

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1 **exon 4 is used as a reference sequence to which the**
2 **sequencing results from the experiment in Example 4 are**
3 **compared.**
4 Q. Okay. If we can go back to your declaration
5 and specifically if we looked at paragraph 512.
6 **A. Okay.**
7 Q. Here, we talked about before that -- this is
8 starting on paragraph 512, you're talking about the
9 obviousness or obviousness arguments based on Bielas,
10 right? You're talking about the obviousness arguments
11 based on Bielas?
12 **A. This paragraph refers to my obvious arguments**
13 **based on Bielas.**
14 Q. Okay. And the specific limitations that you
15 talk about in your obviousness analysis are in paragraph
16 513, you talk about the sample indexing and multiplexing
17 limitations, right?
18 **A. I see that.**
19 Q. And then in paragraphs 514 through 519, the
20 limitations you talk about in those paragraphs are the
21 limitations related to the length of the identifier
22 site; is that accurate?

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1 **A. Those paragraphs discuss the length of the**
2 **identifier site.**
3 Q. And you did not provide any other analysis
4 regarding whether the identifying duplicates limitation
5 of Claim 1 would have been obvious, correct?
6 **A. Those are the two major arguments related to**
7 **obviousness described in this section.**
8 Q. And there's no discussion about the obviousness
9 of the identifying duplicates limitations, correct?
10 **A. There is quite a bit of discussion here about**
11 **the de-duplication process in Bielas as relates to the**
12 **length of the identifier site.**
13 Q. Okay. But are you -- have you taken the
14 position in your declaration that to the extent Bielas
15 does not disclose the identifying duplicates limitation
16 of the challenged claims, that it would have been
17 obvious to a person of ordinary skill in the art?
18 **A. The title of the section is, to the extent that**
19 **Bielas does not anticipate Claim 1, Claim 1 would have**
20 **been obvious based on Bielas. So that statement**
21 **encapsulates all of Claim 1.**
22 Q. And I'm asking, did you address the identifying

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1 duplicates limitation in your obviousness analysis?
2 **A. This section does not have a specific**
3 **discussion about Claim 1D, but my opinion is that all of**
4 **Claim 1 would have been obvious based on Bielas.**
5 **There's a statement here --**
6 Q. Where are you?
7 **A. Sorry.**
8 Q. Okay.
9 **A. One second. To the extent that Example 1 --**
10 **sorry. I'm looking at paragraph 512.**
11 Q. Okay.
12 **A. "To the extent that Example 1 and Example 3 do**
13 **not teach every element of Claim 1 arranged as in the**
14 **claim so as to anticipate Claim at a minimum, Bielas**
15 **renders Claim 1 obviousness for the same reasons I**
16 **discuss above," I won't read the section numbers but**
17 **they're there, so the anticipation -- I'm applying the**
18 **anticipation argument to an assessment of obviousness in**
19 **this statement.**
20 Q. And just to confirm, you don't specifically
21 call out the obviousness of the identifying duplicates
22 limitation in this obviousness section that starts at

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1 512, paragraph 512, right? You just rely on your
2 previous discussion of that limitation?
3 **A. In this section, I refer specifically to other**
4 **sections and apply them to my assessment of obviousness.**
5 **Those sections have very detailed discussions of the**
6 **limitations of, for example, Claim 1D.**
7 Q. Sure, and I understand that. I'm saying, you
8 refer to other sections in your declaration, you also
9 call out specific limitations in the obviousness section
10 of your declaration and talk about why those would have
11 been obvious.
12 The identifying duplicates limitation are not
13 included in those additional limitations that you call
14 out in your obviousness analysis, correct?
15 **A. There isn't a detailed discussion of Claim 1D**
16 **in this section, where I'm analyzing obviousness. This**
17 **section focuses on other limitations.**
18 MS. CIPRIANO: Okay. It might be a
19 good time to take a break.
20 MR. FLETCHER: We can go off the
21 record.
22 (Time Noted: 4:05 p.m.)

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1 A C K N O W L E D G M E N T
2
3 STATE OF NEW YORK)
:ss
4 COUNTY OF QUEENS)
5
6 I, PETER SIMS, Ph.D., hereby certify that I
7 have read the transcript of my testimony taken under
8 oath in my deposition of the 26th day of June, 2025;
9 that the transcript is a true, complete and correct
10 record of my testimony, and that the answers on the
11 record as given by me are true and correct.
12
13
14 _____
15 PETER SIMS, Ph.D.
16
17 Signed and subscribed to before
me, this day
18 of , 2025.
19
20 _____
Notary Public, State of New York
21
22

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1 C E R T I F I C A T E
2 I, BROOKE E. PERRY, Certified Reporter and Notary
Public within and for the State of New York, do hereby
3 certify:
That PETER SIMS, Ph.D., the witness whose deposition
4 is hereinbefore set 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 party, TECAN
GENOMICS, INC., was represented by counsel at the
7 deposition.
I further certify that the deposition of PETER
8 SIMS, Ph.D., occurred at the offices of Williams &
Connolly LLP 650 Fifth Avenue Suite 1500 New York, NY
9 10019 on Thursday, June 26, 2025, commencing at
9:15 a.m. to 4:05 p.m.
10 I further certify that I am not related to any
of the parties to this action by blood or marriage,
11 I am not employed by or an attorney to any of the
parties to this action, and that I am in no way
12 interested, financially or otherwise, in the outcome
of this matter.
13 IN WITNESS WHEREOF, I have hereunto set my hand
this 30th day of June, 2025.
14
15 Brooke E. Perry
_____
16 BROOKE E. PERRY
17
18
19
20
21
22

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1 ERRATA SHEET
2 CASE NAME: INTEGRATED DNA TECHNOLOGIES, INC. V.
3 TECAN GENOMICS, INC.
4 DATE OF DEPOSITION: June 26, 2025
5 WITNESS'S NAME: PETER SIMS, Ph.D.
6
7 PAGE LINE (S) CHANGE REASON
8 ____|_____|_____|_____
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22

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1 PETER SIMS, Ph.D.
2
3 SUBSCRIBED AND SWORN TO BEFORE ME
4 THIS ____ DAY OF _____, 20__.
5 _____ _____
6 (NOTARY PUBLIC) MY COMMISSION EXPIRES:
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