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Transcript of Peter A. Sims, Ph.D., Volume 2

Date: June 27, 2025

Case: Integrated DNA Technologies, Inc. -v- Tecan Genomics, Inc. (PTAB)

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WORLDWIDE COURT REPORTING & LITIGATION TECHNOLOGY

Transcript of Peter A. Sims, Ph.D., Volume 2
Conducted on June 27, 2025

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1 UNITED STATES PATENT AND TRADEMARK OFFICE 2 BEFORE THE PATENT TRIAL AND APPEAL BOARD 3 -----x 4 INTEGRATED DNA TECHNOLOGIES, INC., Case IPR Nos: 5 6 IPR2024-01502 7 Petitioner, U.S. Patent 9,546,399 8 IPR2024-01504 9 U.S. Patent 11,098,357 10 -against- IPR2024-01506 11 U.S. Patent 11,725,241 12 IPR2025-00015 13 TECAN GENOMICS, INC., U.S. Patent 10,036,012 14 IPR2025-00016 15 Patent Owner. U.S. Patent 10,876,108 16 -----x 17 CONTINUED DEPOSITION of PETER SIMS, PH.D., 18 taken by the Patent Owner, pursuant to Notice, held at 19 the law offices of Williams & Connolly LLP, 650 5th 20 Avenue, Suite 1500 New York, NY 10019, on June 27, 2025, 21 at 8:54 a.m., before a Notary Public of the State of New 22 York.	1 INDEX 2 WITNESS EXAMINATION BY PAGE Peter Sims, Ph.D. Linnea Cipriano 148 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
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1 A P P E A R A N C E S : 2 WILLIAMS & CONNOLLY LLP Attorneys for Petitioner 680 Maine Avenue SW Washington, DC 20024 3 4 BY: KEVIN HOAGLAND-HANSON, ESQ. khoagland-hanson@wc.com THOMAS FLETCHER, ESQ. ANNA SEARLE, ESQ. 5 6 7 8 9 GOODWIN PROCTER LLP Attorneys for Patent Owner The New York Times Building, 620 Eighth Avenue New York, NY 10018 10 11 BY: LINNEA P. CIPRIANO, ESQ. lcipriano@goodwinlaw.com TIMOTHY BEAVERS, ESQ. SOPHIA VAUGHAN, ESQ. 12 13 14 15 ALSO PRESENT: 16 MICHAEL LEVY- Danaher 17 18 19 20 21 22	1 (Whereupon, the witness was reminded of his 2 sworn oath.) 3 EXAMINATION BY 4 MS. CIPRIANO: 5 Q. Welcome back, Dr. Sims. 6 A. Good morning. 7 Q. Okay. So we were going to switch our 8 conversation from yesterday to today, focusing on your 9 declaration that was submitted as Exhibit 1085. Do you 10 have that in front of you? 11 A. I have that in front of me. 12 Q. Okay. Great. So if we could take a look at 13 paragraph 30. And in this paragraph you provide a 14 high-level summary of the subject matter of the '012 and 15 the '108 patents; is that accurate? 16 A. I see that, yes. 17 Q. And just so we're on the same page, you say the 18 '012 and the '108 patents, the enrichment patents, 19 generally relate to a method for generated a selectively 20 enriched library of DNA molecules for sequencing using a 21 next generation sequencing NGS platform. 22 A. I see that.

149 1 Q. And then you go and you say: 2 "The library is selectively enriched 3 for a particular sequence of interest." 4 Do you see that? 5 A. I see that. 6 Q. When you refer to a "library," and later in 7 that sentence, you also call it a "sequencing library," 8 you're referring to a mixture of DNA or RNA molecules in 9 the sample that will be sequenced; right? 10 A. What I would want to clarify is that it's 11 possible that not all of the molecules or fragments in a 12 sample would end up actually being sequenced. 13 Particularly if an enrichment strategy is employed, it's 14 possible that some of them might not be sequenced. But 15 in general, I'm referring to a sample that contains 16 sequences of interest that -- some of which might be 17 sequenced. 18 Q. But so we're on the same page, this is the -- 19 these are the nucleic acid fragments that make up the 20 library; right? 21 A. Can you clarify what you mean by "these"? 22 Q. Sure. I want to make sure that we understand	151 1 Q. When you say "relative to others," that's 2 relative to others -- other molecules in the same 3 mixture; is that right? 4 MR. HOAGLAND-HANSON: Objection. Form. 5 A. So, for example, one might start out with a 6 sample that is a mixture of nucleic acid fragments, and 7 at the conclusion of an enrichment procedure, some of 8 the nucleic acid fragments occur at a higher frequency 9 and are therefore over -- overrepresented relative to 10 others in the original mixture. 11 Q. Okay. If we could to turn to paragraph 80 of 12 your declaration, that's Exhibit 1085. 13 A. I'm there. 14 Q. In this section you talk about -- the section 15 is labeled "Next Generation Sequencing." In this 16 initial couple of paragraphs, you talk about the initial 17 development of next generation platforms; is that fair? 18 A. That's what I discuss in these paragraphs, 19 the -- the development of sequencing technology and the 20 transition to NGS technology. 21 Q. And you were not personally working on next 22 generation sequencing technologies when they were first
150 1 that the "library" is a mixture of nucleic acids. That 2 is what makes up a library; correct? 3 A. The library is comprised of nucleic acids. 4 Q. Okay. And then when you said that some 5 portions of the library may not be sequenced if an 6 enrichment strategy is employed, can you explain what 7 you meant by that? 8 A. Depending on the design of the enrichment 9 strategy, it's possible, for example, for some sequences 10 to be insufficiently amplified to be readily sampled for 11 sequencing in the final step. So, for example, some 12 sequences in the library could be depleted to the extent 13 that they're not sequenced. 14 Q. And you -- in paragraph 30 you use the term 15 "selectively enriched." Do you see that? 16 A. I see that. 17 Q. What do you mean by "selectively enriched"? 18 A. The specification of the enrichment patents do 19 not provide a quantitative definition of enriched or 20 enrichment, but my interpretation is that "enriched" in 21 this context refers to overrepresentation of certain 22 nucleic acids in a library relative to others.	152 1 developed in the mid 2000s; right? 2 A. I developed an NGS technology in graduate 3 school. I worked on it starting in 2007, although 4 several NGS technologies had already become commercially 5 available by that time. 6 Q. Okay. And thinking about your work with NGS 7 technologies in the 2007 timeframe, would you agree that 8 the field was rapidly developing new methods associated 9 with these NGS technologies? 10 A. The -- the field was rapidly developing 11 applications and methods surrounding these NGS 12 technologies, and also there was development of the 13 sequencers themselves during that time. 14 Q. And in your experience, were researchers during 15 that 2007, late 2000s timeframe trying to combine what 16 they knew about pre NGS library preparation techniques 17 with the next generation sequencing platform? 18 A. There are certainly some commonalities between 19 methods used for earlier stage sequencing technologies, 20 like Sanger sequencing and what's used in NGS. But I 21 would also say that NGS presented completely novel 22 advantages over Sanger sequencing. And so scientists

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153 1 developed completely new methods that were really only 2 useful given the advances from NGS. 3 Q. And off the top of your head, sitting here now, 4 do you know of any pre-next generation sequencing 5 library preparation techniques that were not compatible 6 with next generation sequencing platforms? 7 MR. HOAGLAND-HANSON: Objection. Form. 8 A. This question is very application and platform 9 specific, but I can -- I give a -- one example. The 10 Illumina sequencer, for example, might struggle to 11 amplify extremely long pieces of DNA that could be still 12 sequenced with Sanger sequencing. 13 Q. Can you think of any other examples? 14 MR. HOAGLAND-HANSON: Same objection. 15 A. I can think of some sort of trivial example 16 like the different NGS platforms require the use of 17 specific adaptor sequencers, and so a library 18 construction method that did not employ compatible 19 adaptor sequences could fail to sequence on a particular 20 NGS platform. 21 Q. And anything else you can think of? 22 MR. HOAGLAND-HANSON: Same objection.	155 1 paragraph 89, I draw a comparison to the Illumina 2 platform where the process of clonal amplification is, 3 essentially, fully automated. And so in the 454 4 platform, the experimenter has to do this process 5 himself or herself, whereas a machine takes care of it 6 for you on the Illumina platform, and so that's nice. 7 Q. And about how long did that process take, the 8 hands-on part of that amplification for the 454? 9 A. I don't recall exactly how long it took. Both 10 the 454 clonal amplification process and, for example, 11 the Illumina clonal amplification process are -- are 12 using similar, but subtly different amplification 13 schemes, and my impression is that they take similar 14 amount of time. It's just that one of them, the 15 Illumina one, is more automated. 16 Q. And you were talking about your personal 17 experience with the 454 sequencer. What sort of project 18 were you working on when you were using the 454 19 sequencer? 20 A. The instrument was purchased in the lab where I 21 was performing my graduate studies for a different 22 project, not for the project I was working on. I was
154 1 A. Sitting here today, those are -- those are the 2 two that come to mind. 3 Q. Okay. So let's flip ahead to your section on 4 the specific NGS platforms that you discuss and that are 5 in the prior art that we have in this case, that's -- 6 just for reference -- starts on paragraph 86. And the 7 first NGS platform that you discuss in your declaration 8 is the "Roche 454 pyrosequencing platform." Do you see 9 that? 10 A. Sorry? 11 Q. It's paragraph 87. 12 A. I see that, yes. 13 Q. Okay. And in paragraph 89, on the next page, 14 in the first sentence, you describe this platform as 15 "cumbersome and inconvenient." 16 Can you explain what -- what made the 454 17 platform "cumbersome and inconvenient"? 18 A. It worked well, but it wasn't fun to use in my 19 personal experience, in fact. Emulsion PCR requires the 20 experimenter to work with aqueous oil emulsions in -- in 21 rather large volumes. And so I think in this section -- 22 actually, you know, in the first sentence of	156 1 working on -- in parallel, on the development of my own 2 sequencing technology, and so I did some experiments on 3 the 454 genome sequencer, sort of, to understand what 4 the competition looked like. And so I didn't perform 5 any experiments with the 454 sequencer that were 6 published. I wanted to gain experience with how these 7 other platforms worked because I was trying to develop a 8 competing platform. 9 Q. I mean, is it fair to say you were trying to 10 see what you could improve upon? 11 A. I was interested in opportunities to improve 12 various sequencing technologies, but I also knew that 13 these were successfully commercialized instruments. So 14 I -- I think my goal was more to learn from the success 15 of these commercially available platforms as I was 16 developing my own prototype. 17 Q. So in that same paragraph that we're looking 18 at, paragraph 89, you indicate that you switched to 19 using the Illumina platform in -- I think the date you 20 give is 2011; is that -- is that accurate? 21 A. I started using the Illumina platform for 22 projects around 2011.

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157 1 Q. Okay. 2 A. That's accurate. 3 Q. And then you say that: 4 "The advantages of the Illumina 5 platform outweighed the longer read lengths of 6 the 454." 7 Do you see that at the end of that 8 paragraph? 9 A. I see that. 10 Q. What were the advantages of the Illumina 11 platform that you're discussing here? 12 A. The principal advantage of the Illumina HiSeq 13 2000 over the 454 genome sequencer was throughput. You 14 could sequence many more reads in parallel with the 15 HiSeq 2000 than with the 454 genome sequencer. 16 Q. Now, in your experience, did the field as a 17 whole make the shift to Illumina sequencers along with 18 your preference or -- I'll stop -- let me rephrase the 19 question. 20 Did the field as a whole, geneticists looking 21 at genetic sequencing, make the shift to preferring 22 Illumina sequencers over the 454 platform around the	159 1 I'd like to talk a little bit about how the 454 2 sequencer works at a high level. And in paragraph 90, 3 you start to talk about how the actual sequencing data 4 is gathered. Do you see that? 5 A. I see that. 6 Q. And at the bottom of the page, so paragraph 90, 7 at the bottom of page 63, you use a term called 8 "pyrosequencing." Do you see that? 9 A. I see that. 10 Q. What is "pyrosequencing"? 11 A. Pyrosequencing refers to a class of sequencing 12 technologies where the release of pyrophosphate during 13 nucleotide incorporation is detected in order to 14 sequence nucleic acids. 15 Q. And you talk about the 454 sequencing process, 16 that it needs to be imaged in real time. What do you 17 mean by "real time"? 18 A. In the particular version of pyrosequencing 19 that is implemented by 454, the signal from nucleotide 20 incorporation is transient. As a result, one must use a 21 detector that monitors all of the sequencing reactions 22 simultaneously to ensure that one does not miss this
158 1 same time as you did? 2 A. There were certain applications where the 454 3 sequencer still had advantages over the Illumina 4 sequencer. I can't recall the date right now, but at 5 some point around this time period, the 454 sequencer 6 was no longer commercially available. And so around 7 this time, there came a point where we had no choice but 8 to switch to alternatives. 9 Q. And I think yesterday you said that the next 10 generation platform -- or -- that you developed, was it 11 commercially available in China? Is that -- do I -- am 12 I remembering that correctly? 13 A. It has been improved significantly from what I 14 built as a graduate student in the lab, but indeed my 15 Ph.D. advisor moved back to China and started a company 16 that commercialized the technology. 17 Q. Is there a reason you don't use that technology 18 in your lab? 19 A. The commercial version of the technology is not 20 available in the United States for reasons that you 21 might be able to imagine, and I'll leave it at that. 22 Q. Understood. Okay.	160 1 transient event. 2 Q. And you called this real-time analysis a 3 limitation of the 454 platform; is that accurate? 4 A. This feature of the 454 platform is a 5 limitation for some applications. In particular, it 6 limits the throughput of the sequencer, and so 7 applications that require a lot of sequencing suffer as 8 a result. 9 Q. And can you give me an example of an 10 application that would require a lot of sequencing? 11 MR. HOAGLAND-HANSON: Objection to 12 form. 13 A. My perspective on a lot has changed over time 14 as the throughput of the sequencing technologies has 15 grown exponentially. But, for example, de novo assembly 16 of a human genome requires a lot of sequencing. 17 Q. Now, in the 2011 timeframe, would your 18 assessment of a "lot of sequencing" have been the same? 19 A. By 2011, NGS platforms had differentiated 20 themselves on the basis of throughput. So the Illumina 21 HiSeq 2000 had markedly higher throughput than, for 22 example, the 454 platform. And so it's fair to say that

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161 1 around that time, there was divergence in terms of 2 throughput among the different technologies. 3 Q. Okay. Then in paragraph 91, you use the term 4 "homopolymer." And I think we talked about this a 5 little bit yesterday, but let's make sure we're on the 6 same page. What do you -- what are you referring to as 7 a "homopolymer" here? 8 A. A homopolymer is a nucleic acid sequence where 9 the same nucleotide occurs multiple times in a row. So, 10 for example, TTT would be a 3-nucleotide homopolymer. 11 Q. And is it fair to say that homopolymers caused 12 problems with the 454 platform? 13 A. Long homopolymer stretches caused problems for 14 the 454 platform in that the accuracy of sequencing was 15 lower for those types of sequences. 16 Q. So you say that the -- 17 "This higher intensity signal can only 18 be precisely quantified for fewer than 10 19 consecutive nucleotides." 20 Do you see that? 21 A. I see that. 22 Q. So can you explain what happens on the 454	163 1 attribute lower confidence to those reads. 2 Q. Can you give me an example of an application 3 where sequencing accuracy in the homopolymer regions is 4 crucial? 5 A. One might be interested in detecting 6 single-nucleotide polymorphisms in loci that contain 7 such a homopolymer. That might be an inappropriate 8 application of the 454 platform compared to other NGS 9 platforms. 10 Q. So you said earlier that the -- the 454 11 collects information on a lot of -- a lot of samples at 12 the same time; is that fair? 13 A. The 454 platform has different modalities. In 14 general, it can sequence many nucleic acid fragments in 15 parallel, although sometimes they all originate from one 16 sample. In other cases, there are multiple samples 17 mixed together and sample indexes can be used to 18 distinguish the sample of origin for each read. 19 Q. Okay. So apologies. My vocabulary was 20 imprecise there. So the 454 is collecting sequencing 21 information on a number of nucleic acid fragments at the 22 same time; is that accurate?
162 1 machine when there are more than 10 consecutive 2 nucleotides? 3 A. In the 454 platform, when DNA Polymerase 4 encounters a homopolymer stretch with, for example, 11 5 consecutive nucleotides that are the same, it will 6 incorporate those 11 nucleotides, but the signal that's 7 produced by the machine and imaged by the camera might 8 be difficult to discern from the case that, for example, 9 10 nucleotides had been incorporated. And so it's a 10 matter of accurately discerning the length of the 11 homopolymer for long homopolymers. 12 Q. If a sequencing reaction was done on the 454 13 platform and the data showed that there were 14 homopolymers that were 10 or longer, is there a typical 15 way that that data is processed when homopolymers are 16 detected? 17 MR. HOAGLAND-HANSON: Objection. Form. 18 A. The way in which that data would be processed 19 is very application-specific. For example, in some 20 applications, this would not be a major problem. In 21 other applications where sequencing accuracy in such 22 regions of a nucleic acid fragment is crucial, one might	164 1 A. Multiple nucleic acid fragments are sequenced 2 simultaneously on the 454 platform. 3 Q. And some of those nucleic acid fragments might 4 have homopolymers, but not all will have homopolymers; 5 is that fair? 6 A. This depends entirely on the content of the 7 sample being sequenced, but it's certainly possible for 8 some applications for homopolymers to be present. 9 Q. Okay. So let's operate in a hypothetical where 10 in a particular sequencing reaction, there are nucleic 11 acid fragments, some that contain homopolymers and some 12 that do not contain homopolymers. Are you with me? 13 A. I understand. 14 Q. On the 454 platform, would the presence of the 15 homopolymers longer than 10 in a row have an impact on 16 any of the other nucleic acid fragment sequences that 17 are nearby in the sequencing platform? 18 MR. HOAGLAND-HANSON: Objection. Form. 19 A. Can you clarify what you mean by "nearby"? 20 Q. Sure. And maybe it would help to talk about -- 21 so the 454, you said, involves attaching nucleic acid 22 fragments to beads; correct?

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165 1 A. Nucleic acids are attached to beads in the 454 platform. 3 Q. And those beads are put on -- attached to a 4 glass slide before they are put into the 454 machine; 5 correct? 6 A. My recollection is that the 454 sequencer uses an array of etched optical fibers in a bundle. So there are these little micro-wells at the tip of an optical fiber, and the beads go into the wells. 10 Q. Okay. So is it -- is it individual beads that 11 go into individual wells? 12 A. The platform is designed so that one bead can fit in a well, although I think sometimes there are imperfections. 15 Q. Sure. So what I'm trying to get at is if one 16 bead has a homopolymer that is more than 10 of the same 17 nucleotides in a row, does that -- for lack of a better 18 term -- that bright light or bright signal impact any of 19 the beads that are surrounding that bead with the 20 homopolymer? 21 A. My understanding is that the instrument is designed to isolate the signal from each bead as much as	167 1 homopolymer issues that we were discussing related to the 454 platform. 3 Q. Were there any other advantages of the Illumina 4 platform? 5 A. It was less expensive to run. 6 Q. Any others you can think of? 7 A. I think those were the main advantages. 8 Q. Okay. In paragraph 96, the last couple of 9 sentences, you mention that the physical size of the 10 optical imager was a constraint of the 454. Do you 11 see that? 12 A. I see that. 13 Q. In what way was the size of the optical imager 14 a constraint of the 454? 15 A. This goes back to the throughput difference between the Illumina platform and the 454 platform. Because the transient signal from 454 pyrosequencing required real-time detection, the detector in 454 had to be, essentially, the same size as the sample -- or at least match to the size of the sample. And so that limited the throughput of the 454 platform, because you couldn't have a camera that was big enough to see the
166 1 possible, but I don't have extremely detailed knowledge of all of the scenarios in which that might have limitations. 4 Q. Okay. The next sequencing platform you talk 5 about is the "Solexa Illumina Reversible Terminator Sequencing." Do you see that? 7 A. I see that. 8 Q. And that's what we've been referring to as the 9 "Illumina platform"? 10 A. We refer to that as the "Illumina platform," yeah. 12 Q. Okay. Other than being more hands-off or 13 automated, were there additional advantages of the 14 Illumina platform over the 454? 15 A. Can you repeat the question? Sorry. 16 Q. Sure. So I think you said that the Illumina 17 machine was more hands-off than the 454, and you also 18 mentioned that the Illumina platform had -- had higher 19 throughput than the 454. Were there any other 20 advantages of the Illumina platform over the 454 21 platform? 22 A. The Illumina platform did not suffer from the	168 1 number of fragments that could be sequenced with an Illumina machine. 3 Q. I understand. So next you discuss the Ion 4 Torrent. I guess the title is "Life Technologies Ion 5 Torrent Semiconductor Sequencing." 6 A. I see that. 7 Q. Can we just refer to that as "Ion Torrent 8 platform"? 9 A. Okay with me. 10 Q. Now, relative to the 454 and Illumina 11 platforms, how widely used was the Ion Torrent platform 12 in the 2011/2012 timeframe? 13 A. I don't have detailed knowledge on how broadly sold the Ion Torrent sequencer was. It may have been comparable to the 454 platform, if not more utilized, but it was less widely used than the Illumina platform. 17 Q. Were there challenges to working with the Ion 18 Torrent platform? 19 A. The Ion Torrent platform also used emulsion PCR, like the 454 platform; however, Life Technologies did manage to automate the emulsion PCR process to a larger extent. I recall an instrument called the "Ion

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169 1 Chef" that would implement emulsion PCR. 2 Q. They knew what their customers wanted; right? 3 Now, you mentioned in paragraph 98, that the 4 Ion Torrent platform does not involve optical imaging. 5 Do you see that? 6 A. I see that. 7 Q. What -- how -- what kind of detection does the 8 Ion Torrent use? 9 A. The Ion Torrent platform uses a semiconductor 10 that can detect small changes in pH that result from 11 nucleotide incorporation. 12 Q. Does the Ion Torrent platform collect this data 13 in the way that we've been using it, realtime? 14 A. The Ion Torrent platform also collects data in 15 realtime. 16 Q. Okay. So if we could turn to paragraph 125 of 17 your declaration. 18 A. Okay. 19 Q. And I'd like to walk through the challenged 20 claims as you have them laid out in this section of your 21 declaration. So in paragraph 125, in the section that 22 follows, we're talking about claim 1 of the '012 patent;	171 1 polynucleotide that's compatible with ligation. 2 Q. Okay. The -- the next phrase in the limitation 3 A of the claim is "ligated to a partial duplex adaptor." 4 Do you see that? 5 A. I see that. 6 Q. And do you interpret this to mean that adaptors 7 are ligated to both ends of the fragment? 8 MR. HOAGLAND-HANSON: Objection. Form. 9 A. My interpretation is that ligation need not 10 occur on both ends. 11 Q. Now, the next phrase of the claim limitation is: 12 "Wherein the nucleic acid fragment 13 comprises a nucleic acid sequence of interest." 14 Do you see that? 15 A. I see that. 16 Q. Now, how do you interpret "sequence of 17 interest" here? 18 A. I discuss this term, "sequence of interest," in 19 paragraph 133 of my declaration, where I discuss how the 20 specification of the '012 patent uses the terms, "target 21 sequence," "target nucleic acid sequence," "target 22 nucleotide sequence," "sequence of interest,"
170 1 right? 2 A. Claim 1 of the '012 patent is what's discussed 3 there. 4 Q. Okay. So if we look at the -- the enumerated 5 elements of the claims, starting with the one that's 6 labeled "A." Do you see that? 7 A. I see that. 8 Q. All right. So "obtaining a nucleic acid 9 fragment," would you agree that this element of the 10 claim requires that there is a fragment that is a 11 section of a nucleic acid molecule that is shorter than 12 what was originally extracted from a cell? 13 MR. HOAGLAND-HANSON: Objection to 14 form. 15 A. My interpretation of the term "nucleic acid 16 fragment" is broader than that. I'm not sure that a 17 nucleic acid fragment even needs to originate from a 18 cell. 19 Q. Okay. Understood. So when you were analyzing 20 this limitation, how did you understand "nucleic acid 21 fragment" to be used in the claims? 22 A. In this context, a nucleic acid fragment is a	172 1 interchangeably; and "target sequence" is described as a 2 polynucleotide sequence of interest for which enrichment 3 is desired. This statement also points out that the 4 target sequence may be known or not known in terms of 5 its actual sequence. 6 Q. But thinking about performing the method of the 7 '012 patent in -- in real life and not in a -- in a 8 patent claim, a sample on which this method is performed 9 would have fragments, nucleic acid fragments, that 10 contain the sequence of interest and those that do not 11 contain the sequence of interest; right? 12 A. One could apply the methods described in the 13 '012 patent to a sample that contains both sequences of 14 interest and sequences that are not of interest. 15 Q. Doesn't it necessarily have to be that the 16 sample contains both sequences of interest and sequences 17 not of interest? 18 A. I think the methods described in the '012 19 specification would be commonly applied to situations 20 where there was both sequences of interest and sequences 21 that are not of interest, but the methods would still 22 function even if there was only a sequence of interest

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173 1 present. 2 Q. But in order for something to be enriched, 3 there has to be a comparator that is not enriched; 4 right? 5 MR. HOAGLAND-HANSON: Objection. Form. 6 A. The term "enriched" typically applies to 7 situations where there are sequences that are enriched 8 and sequences that are not enriched or less enriched. 9 Q. And that's how you used the term "enriched"; 10 correct? 11 MR. HOAGLAND-HANSON: Objection. Form. 12 A. Earlier in our discussion, I gave my 13 interpretation of how the term "enriched" is used in 14 this context, and I think I said that it refers to 15 situations where a -- an enrichment process results in 16 overrepresentation of certain nucleic acid sequences 17 relative to others in a sample. 18 Q. So the rest of the limitation A of Claim 1: 19 "Wherein the partial duplex adaptor 20 comprises a first adaptor sequence, and wherein 21 the partial duplex adaptor comprises a first 22 strand and a second strand wherein the first	175 1 oligonucleotides comprise a 3' portion with at 2 least 10 bases designed to be complementary to 3 the nucleic acid sequences of interest and a 5' 4 tail portion comprising a second adaptor 5 sequence that is noncomplementary to the 6 nucleic acid sequence of interest." 7 Do you see that? 8 A. I see that. 9 Q. So this means that the -- one or more 10 "oligonucleotides" that's referenced here has a portion 11 that is the complement of the sequence of interest and a 12 portion that is not a complement of the sequence of 13 interest; correct? 14 A. The claim language refers to: 15 "Oligonucleotides where a region of the 16 3' end is complementary to a nucleic acid 17 sequence of interest, and a region of the 5' 18 end is not complementary to the nucleic acid 19 sequence of interest." 20 So the complementary region in the 21 figure on page 82 is the red arrow, and the 22 noncomplementary component on the 5' end is the
174 1 strand is longer than the second strand." 2 That is just referring to the specifics 3 of the adaptor where it's double-stranded and 4 the two strands are different sizes; is that a 5 good summary? 6 A. The adaptors are not entirely comprised of 7 double-stranded DNA. The adaptors are considered 8 partial duplex because one strand is longer than the 9 other, so the duplex portion is only a portion of the 10 longer strand. 11 Q. So if we look at limitation B, now on page 82 12 of your declaration, it talks about the concept of 13 "annealing." Annealing is the process where 14 complementary strands of DNA align and stick together; 15 is that accurate? 16 A. Annealing is the process by which two 17 complementary or partially complementary nucleic acid 18 strands bind to one another via Watson-Crick base 19 pairing. It's also referred to as "hybridization." 20 Q. So there's a wherein clause in the second half 21 of limitation B of Claim 1 and it reads: 22 "Wherein the one or more	176 1 green rectangle. 2 Q. Is it fair to call the oligonucleotide 3 referenced in limitation B a target-specific 4 oligonucleotide? 5 MR. HOAGLAND-HANSON: Objection. Form. 6 A. I think the properties of that oligonucleotide 7 are well-described by the claim. And it's important to 8 point out that there can be multiple sequences of 9 interest in a sample that are -- I'm sorry, for which 10 amplification is facilitated by such an oligonucleotide. 11 Q. Yesterday we talked about an article by 12 Siebert, I think. 13 A. I recall the article by Siebert. 14 Q. And we can get it out again if -- if it's 15 helpful, but my question is fairly general. Siebert 16 talked about using -- maybe I'll have to look, but let's 17 see if we can get on the same page without getting into 18 the details. 19 Siebert talked about using a gene-specific 20 primer; is that -- do you recall that? 21 A. Siebert refers to "gene-specific primers," for 22 example, in the legend of Figure 1A.

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177 1 Q. All right. Just for the record, you're looking 2 at Exhibit 1007? 3 A. I am. I noticed that this document has some 4 writing on it that is not from me, and it didn't 5 yesterday, so I'm not sure I'm looking at the same piece 6 of paper that I had yesterday, but I'm looking at 7 Siebert 10007. But I didn't write on this piece of 8 paper; somebody else did. 9 Q. Okay. Do we have a -- 10 A. Sorry. It's just got some, like, lines on it. 11 Q. -- do we have a clean -- 12 A. Maybe -- yeah, that might be better. It's 13 possible that -- 14 Q. I understand. It's -- 15 A. -- multiple copies got passed around or 16 something. That was, like, at the bottom of my pile 17 from yesterday, but -- I don't think I have a clean 18 Siebert. 19 MR. HOAGLAND-HANSON: We can get a 20 clean copy. 21 A. I've been diligent about not writing 22 stuff; so --	179 1 depicted as a primer in the figure that we drew below 2 it, could be a gene-specific primer, but it doesn't have 3 to be a gene-specific primer. That primer could 4 facilitate amplification of multiple genes; and even if 5 it were designed to be gene-specific, it could also 6 result in amplification of other loci. 7 MS. CIPRIANO: It might be time for a 8 real quick break. 9 THE WITNESS: Okay with me. 10 (Whereupon, a short break was taken.) 11 BY MS. CIPRIANO: 12 Q. Okay. If we could look now at limitation C of 13 Claim 1 of the '012 patent -- we're still in page 82 of 14 Exhibit 1085 -- and the limitation reads: 15 "Extending the one or more 16 oligonucleotides annealed to the nucleic acid 17 sequence of interest in the nucleic acid 18 fragment ligated to the partial duplex adapter 19 with a polymerase, thereby generating one or 20 more oligonucleotide extension products 21 comprising a sequence, complementary to the 22 first adaptor sequence at a first end, a
178 1 Q. Okay. I mean, can I just look at it to see and 2 make sure that -- 3 A. That you're okay with it, yeah. 4 Q. -- you don't have secret notes. 5 A. Yeah, yeah, yeah. 6 MR. HOAGLAND-HANSON: Clearly, Tom has 7 written notes. 8 A. Oh, okay. Okay. Sorry. Sorry. Okay. We're 9 good now. 10 Q. I appreciate your honesty. 11 A. Yeah. Just -- don't want to get in trouble. 12 Q. Okay. So let's get back on track. 13 So Siebert refers to gene-specific primers in 14 the legend of Figure 1A; right? 15 A. I see that. 16 Q. Okay. Would you consider the oligonucleotide 17 described in limitation B of Claim 1 of the '012 patent 18 a gene-specific primer? 19 MR. HOAGLAND-HANSON: Objection. Form. 20 A. So Claim 1B has multiple oligonucleotides 21 floating around in it. The particular oligonucleotide 22 that's highlighted at the end of Claim 1B and that's	180 1 sequence complementary to the nucleic acid 2 sequence of interest and the second adaptor 3 sequence at a second end." 4 So to put that in -- in more 5 understandable language, would you agree that 6 the extension product that is generated from 7 step C of the -- of Claim 1 of the '012 patent 8 includes a sequence complementary to the first 9 adaptor, a sequence of interest and a second 10 adaptor sequence? 11 MR. HOAGLAND-HANSON: Objection. Form. 12 A. Could you rephrase the question? It was a 13 little long for me to parse. 14 Q. Sure. So -- we'll take it in steps. 15 Limitation C requires the generating of an 16 extension product; correct? 17 A. In limitation C an oligonucleotide primer is 18 extended with a polymerase. 19 Q. And when that oligonucleotide primer is 20 extended with a polymerase, it generates what's called 21 an "extension product"; correct? 22 A. Claim 1C states that extending the one or more

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181 1 oligonucleotides generates one or more oligonucleotide 2 extension products. 3 Q. And those extension products contain a sequence 4 complementary to the first adaptor sequence, a sequence 5 complementary to the sequence of interest and a second 6 adaptor sequence; correct? 7 A. Oligonucleotide extension products comprise a 8 sequence complementary to the first adaptor sequence, 9 which is the blue sequence in the figure drawn below; a 10 sequence complementary to the nucleic acid sequence of 11 interest, which is drawn in red; and a second adaptor 12 sequence at the second end, that's the green sequence. 13 This Claim uses the word "comprising," so that means 14 it's not limited to those aspects. 15 Q. So at the end of the step of the method that is 16 described in limitation C, the only fragments in the 17 mixture to have a sequence complementary to the first 18 adaptor sequence, a sequence complementary to the 19 nucleic acid sequence of interest and the second adaptor 20 sequence will be the extension products; is that 21 accurate? 22 MR. HOAGLAND-HANSON: Objection. Form.	183 1 the only sequence in the mixture -- the only fragments 2 in the mixture that would have all three of a sequence 3 complementary to the first adaptor sequence, a sequence 4 complementary to the nucleic acid sequence of interest, 5 and a second adaptor sequence would be the extension 6 products; right? 7 MR. HOAGLAND-HANSON: Objection. Form. 8 A. Formally speaking, there could be other 9 oligonucleotides in the mixture that have that same 10 composition. They could be present even prior to 11 performing this method. The composition -- the detailed 12 composition of the nucleic acid mixture is not specified 13 by the claim. 14 Q. Would this method work if the adaptor sequences 15 used in -- referred to in the claims were present 16 throughout other and all of the nucleic acid fragments 17 in the mixture? 18 MR. HOAGLAND-HANSON: Objection. Form. 19 A. That would be -- that would depend on the 20 details of what the sequences of those adaptors were and 21 many other variables. I don't think I can definitively 22 answer that.
182 1 A. Can you repeat that question, please? Sorry. 2 Q. So at the end of the step of the method that is 3 described in limitation C, the only fragments in the 4 mixture to have a sequence complementary to the first 5 adaptor sequence, a sequence complementary to the 6 nucleic acid sequence of interest and a second adaptor 7 sequence will be the extension products; is that 8 accurate? 9 MR. HOAGLAND-HANSON: Objection. Form. 10 A. I don't think that Claim 1C is comprehensively 11 commenting on all of the possible reactions that could 12 be occurring in a -- in a mixture. It's just describing 13 a particular oligonucleotide extension product that 14 results from this procedure. 15 Q. So I'm not asking about what the comprehensive 16 commenting on -- on the reactions that could happen. 17 I'm saying, if you were to perform this method in your 18 laboratory, your expectation would be that the only 19 sequences -- the only -- excuse me, let me start over. 20 If you were to perform this method in your 21 laboratory, your expectation would be that after step C 22 of the method described in Claim 1 of the '012 patent,	184 1 Q. Adaptors, as commonly used in next generation 2 sequence methods, are typically synthetic sequences that 3 are not present in the genome that is being tested; is 4 that fair? 5 A. Adaptors are -- adaptors used in NGS are 6 typically synthetic oligonucleotides, but I don't know 7 comprehensively whether or not they can occur in other 8 samples or genomes of other organisms. They have a lot 9 of sequence content and there could certainly be some 10 overlap. 11 Q. The goal of using an adaptor is to introduce 12 a -- a nucleic acid sequence that you can use and target 13 in the method, would you agree? 14 A. Adaptors in NGS are used for many things, 15 including to facilitate amplification of nucleic acid 16 fragments, to facilitate hybridization of sequencing 17 primers to nucleic acid fragments. They do not always 18 work perfectly. The Illumina sequencing adaptors, for 19 example, were selected a long time ago, and it's 20 certainly possible for components of those sequences to 21 occur in samples of interest. 22 Q. So going back to our extension product

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185 1 discussion: What is the likelihood that there are 2 nucleic acid fragments in a mixture that contain all 3 three of a sequence complementary to the first adaptor 4 sequence at a first end, a sequence complementary to the 5 nucleic acid sequence of interest and a second adaptor 6 sequence at a second end that are not the extension 7 products? 8 MR. HOAGLAND-HANSON: Objection. Form. 9 A. I don't know how to calculate the probability 10 of that. 11 Q. It's pretty low; right? 12 MR. HOAGLAND-HANSON: Same objection. 13 A. There isn't a clear definition here of what the 14 nucleic acid sample under study is. There are a lot of 15 nucleic acid samples to which this method could be 16 applied. 17 Q. So it's your opinion that the extension product 18 that is generated at the end of the limitation step C of 19 Claim 1 of the '012 patent is not the only sequence -- 20 no. Let me start over. 21 Okay. Let's see if maybe looking at limitation 22 D might help this discussion. If we look at limitation	187 1 Do you see that? 2 A. I see that. 3 Q. So in order to enrich for the nucleic acid 4 sequence of interest, the amplification step needs to 5 amplify the fragments containing the nucleic acid 6 sequence of interest more than other fragments; right? 7 MR. HOAGLAND-HANSON: Objection. Form. 8 A. My interpretation of Claim 1D is that it is 9 part of a process that results in enrichment for the 10 nucleic acid sequence of interest, but doesn't discount 11 the possibility that other things are going on that also 12 lead to enrichment. 13 Q. What do you mean other things "going on that 14 could also lead to enrichment"? 15 A. For one thing, this is a multistep process, and 16 step 1D isn't the only part of that process that is 17 important for achieving enrichment, but the claim 18 doesn't limit or exclude the possibility of implementing 19 other methods to help facilitate enrichment of the 20 sequence of interest. 21 Q. Understood. But you would agree that Claim 1 22 of the '012 patent in step D requires that the
186 1 D, this is the "amplifying step." Do you see that? 2 A. I see that limitation D describes amplifying. 3 Q. And specifically it talks about "amplifying the 4 extension products"; correct? 5 A. It describes amplifying extension products. 6 Q. And the way that it goes about amplifying those 7 extension products is using primers directed to the 8 first adaptor sequence and the second adaptor sequence 9 that we're -- we talked about are in the extension 10 products generated at the end of step C; correct? 11 A. My interpretation of Claim 1D is that it 12 describes an amplification process that uses two 13 primers: one annealing to a first adaptor, and one 14 annealing to a second adaptor. 15 Q. And specifically, the amplification process 16 described in Claim 1D uses those two primers to amplify 17 the extension products generated in step C; correct? 18 A. The amplification process in step D amplifies 19 oligonucleotide extension products described in 1C. 20 Q. And then this -- the next phrase of limitation 21 1D is "to enrich for the nucleic acid sequence of 22 interest."	188 1 amplification of the extension products leads to 2 enrichment of a nucleic acid sequence of interest over 3 other fragments in the mixture; right? 4 A. I agree that amplification in step 1D is part 5 of the enrichment process. 6 MS. CIPRIANO: That's not my question. 7 Q. My question is whether you agree that Claim 1 8 of the '012 patent in step D requires that the step of 9 amplifying the extension products enriches for the 10 nucleic acid sequence of interest over other fragments 11 in the sample. 12 MR. HOAGLAND-HANSON: Objection. Form. 13 A. Amplification is a key step in the enrichment 14 process. I just don't want to claim that it's the only 15 thing going on here. 16 Q. Understood. And this is -- let's set aside the 17 other steps in a potential method that could contribute 18 to enrichment. I just want to look at this limitation 19 1D and confirm that you agree that the amplifying of the 20 extension products must enrich for a nucleic acid 21 sequence of interest over other fragments in the sample. 22 A. I agree that at the conclusion of this

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189 1 amplification process, enrichment must occur. 2 Q. And the amplification process must contribute 3 to cause enrichment of the nucleic acid sequence of 4 interest over other fragments in the mixture; right? 5 A. Amplification contributes to enrichment. 6 Q. Is that a yes? 7 MR. HOAGLAND-HANSON: Objection. Form. 8 A. I agree that amplification contributes to 9 enrichment. 10 Q. Do you agree that the amplification of the one 11 or more oligonucleotides extension products listed in 12 element D of the claim enriches -- must enrich for the 13 nucleic acid sequence of interest over other fragments 14 in the mixture? 15 MR. HOAGLAND-HANSON: Objection. Form. 16 A. I agree that this amplification step 17 contributes to enrichment. 18 Q. What do you mean "contributes to enrichment"? 19 A. The amplification process forms the sequencing 20 library in which the nucleic acid sequence or sequences 21 of interest -- sorry. 22 The amplification process leads to the	191 1 overrepresented at the end of this process, for example, 2 if an earlier process caused overrepresentation of a 3 sequence of interest. 4 Q. So in your opinion, the phrase "amplifying the 5 one or more oligonucleotide extension products to enrich 6 for the nucleic acid sequence of interest" does not 7 require that the amplification step cause enrichment of 8 a nucleic acid sequence of interest; is that correct? 9 MR. HOAGLAND-HANSON: Objection. Form. 10 A. I don't want to discount the importance of the 11 amplification step in -- in 1D or the concept that it 12 contributes to enrichment, but it's possible for the 13 amplification rate of oligonucleotides in the sample to 14 be the same and you can still have overrepresentation 15 for enrichment of nucleic acid sequence or sequences of 16 interest at the end of this process. 17 Q. So the way that you interpreted the claims is 18 that as long as the nucleic acid sequence of interest is 19 enriched in -- at the end of the method, that satisfies 20 the "enrich" element of the claims; is that fair? 21 MR. HOAGLAND-HANSON: Objection. Form. 22 A. This is a method for sequencing an enriched
190 1 formation of the sequencing library containing the 2 enriched nucleic acid sequence or sequences of interest. 3 Q. So in your opinion, if in limitation 1D -- in 4 the amplification step, if all fragments in the mixture 5 are amplified at the same rate, we'll say -- I'm sure 6 there's a better word for it. So if all fragments are 7 amplified at the same rate, could that still meet the 8 limitation of this claim or this -- yeah, this claim. 9 Let me rephrase that; it's a meandering 10 question, apologies. 11 If you were to perform a method of -- along the 12 lines of -- let me start over. 13 If you were to perform a method in which a 14 sample is amplified and all of the nucleic acid 15 fragments are amplified at the same rate, would that, in 16 your opinion, meet the limitation 1D of the '012 patent? 17 A. To satisfy the claim, enrichment must occur, 18 but there are multiple steps in the process comprised 19 here that could contribute to enrichment. So even if 20 the amplification step facilitates amplification of 21 nucleic acid fragments at the same rate, it's possible 22 for some of those nucleic acid fragments to be	192 1 nucleic acid sequence of interest. It's a multistep 2 process, and I don't want to attribute causality that 3 isn't clearly stated in the claim to any one step. 4 They're all important steps that are contributing to 5 enrichment of a nucleic acid sequence of interest. 6 Q. So in your opinion, the term "amplifying to 7 enrich" for a nucleic acid sequence of interest does not 8 indicate causality? 9 MR. HOAGLAND-HANSON: Objection. Form. 10 A. To me it's like boarding a subway car to get to 11 work. The subway has got to move in order for you to 12 get to work, but you board the subway car to get to 13 work; that's how I see "amplifying to enrich." It's a 14 necessary step in this process, but it's not the only 15 thing that contributes to enrichment, necessarily. 16 Q. So in your analogy, boarding a subway car to 17 get to work, the subway car moves you toward work, it 18 causes you to get to work; right? 19 A. The subway car moves you to get to work, but 20 it's not the only thing that causes you to get to work. 21 There's a whole process that causes you to get to work. 22 Q. Sure. But it contributes to your progress

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193 1 toward work; right? You wouldn't get on a subway car to 2 get to work, that wasn't moving; right? 3 A. Unfortunately, I've done that many times, 4 but I -- 5 Q. Not on purpose. 6 A. -- I think we're on the same page here. This 7 is a step in a multistep process. And I'm not going to 8 change my answer that amplification is one of multiple 9 steps that contributes to enrichment. It's not the only 10 step, necessarily, that contributes to enrichment. 11 Q. And I'm just trying to get a clean record that 12 you interpreted the claims in a way that the amplifying 13 performance, step D of the method, did not need to 14 further enrich for the nucleic acid sequence of interest 15 in the sample; is that accurate? 16 MR. HOAGLAND-HANSON: Objection. Form. 17 A. There's nothing in claim D that specifies 18 anything about amplification rates or amplification 19 efficiencies. My interpretation is that amplification 20 is a necessary step in the enrichment process. The 21 extent to which it quantitatively contributes to 22 overrepresentation is not specified by the claim.	195 1 Q. Are those the only steps that can -- where 2 enrichment can occur? 3 A. I haven't formed a carefully considered opinion 4 on where in this process or what -- what steps in this 5 process are the only steps where enrichment could occur. 6 And I would also note that this claim doesn't exclude 7 the possibility of other things taking place in these 8 various steps and reactions that could also contribute 9 to enrichment. 10 Q. Can you please explain to me how enrichment can 11 occur in that method step that's described in 1C? 12 A. In step 1C, a sequence of interest is copied by 13 a polymerase, thus it's abundance increases. 14 Q. So in step 1C, there are going to be certain 15 fragments in the mixture that contain the sequence of 16 interest that are copied, and there are going to be 17 certain nucleic acid fragments that don't contain the 18 sequence of interest that are not going to be copied; 19 right? 20 A. That is not a strict requirement of Claim 1C, 21 but that is one possible outcome of Claim 1C, depending 22 on the situation.
194 1 Q. So in your opinion, if the sample that was used 2 in step A of the method of Claim 1 of the '012 patent 3 had an overrepresentation of the nucleic acid sequence 4 of interest before starting the process of ligating the 5 adaptors and you performed the method on that sample as 6 set forth in the claims, would that meet the enrichment 7 element of these claims? 8 MR. HOAGLAND-HANSON: Objection. Form. 9 A. My interpretation is that Claim 1 describes an 10 enrichment process, and so overrepresentation of a 11 nucleic acid sequence of interest at the beginning of 12 the process doesn't satisfy the claim. The process 13 described here enriches. It's possible that other 14 things are going on that also contribute to enrichment, 15 but the process described here is critical for 16 enrichment. 17 Q. Can you point me to what steps of the method 18 described in Claim 1 of the '012 patent where enrichment 19 could occur? 20 A. Enrichment could occur in step 1C; enrichment 21 could occur in step 1D. Those are examples of places 22 where enrichment could occur.	196 1 Q. But that is the only way that Claim 1C could 2 contribute to enrichment; correct? 3 A. "Contribute to" is a pretty loaded term. I 4 mean, Claim 1C facilitates the inclusion of adaptors. 5 That by itself is important for forming the nucleic acid 6 sequencing library. 7 Q. Okay. Let me rephrase my question. The only 8 way that step 1C could cause enrichment is if there were 9 certain nucleic acid fragments that contained the 10 sequence of interest that are copied and nucleic acid 11 fragments that do not contain the sequence of interest 12 that are not copied; right? 13 A. I disagree. It's all about the extent to which 14 they are copied. It's -- it's not a binary issue, 15 copied or not copied. 16 MR. HOAGLAND-HANSON: Linnea, I don't 17 know how much you have in this line, but there 18 is lunch outside for whenever you want to take 19 a break. I don't know if you want to finish up 20 this topic, push to 12 and then take a break, 21 something like that. 22 MS. CIPRIANO: Okay. Sure. I know

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197 1 we've been going about an hour; so -- 2 MR. HOAGLAND-HANSON: Yeah. Well, if 3 you're good. 4 And, Peter, if you're good. 5 THE WITNESS: I'm okay. I'm okay. I'm 6 just -- 7 BY MS. CIPRIANO: 8 Q. So previously, I asked the question: 9 "Can you please explain to me how 10 enrichment can occur in the method step that is 11 described in 1C?" 12 And your answer -- I'm reading from the 13 rough transcript: 14 "In step 1C a sequence of interest is 15 copied by a polymerase, thus its abundance 16 increases." 17 Do you recall that question and answer? 18 A. I recall that question and answer. 19 Q. So in order for that copying by a polymerase to 20 cause enrichment, there have to be nucleic acid 21 fragments that are not copied by the polymerase; right? 22 A. One way that step 1C could lead to or	199 1 A. This is the Meyer reference discussed in my 2 declaration. 3 Q. Were you aware of this paper before your 4 involvement in this matter? 5 A. I was not aware of this paper before my 6 involvement in this matter. 7 Q. So in your discussion -- in your declaration, 8 you rely on the method that's depicted in Additional 9 File 4 in the Meyer article, is that -- do you recall 10 that? 11 A. My declaration refers to this Additional File 4 12 protocol and the figure contained in it. 13 Q. And the Additional File 4 schematic of the 14 method appears on page 98 of your declaration; correct? 15 A. Page 98 has the figure from Additional File 4. 16 Q. So I don't -- it doesn't matter to me what you 17 refer to, whether it's the -- the figure on page 20 of 18 the Meyer reference Exhibit or the figure in your 19 declaration. Feel free to -- at your -- 20 So I'd like to walk through the figure so we 21 understand what's going on in Meyer. At the top of the 22 figure, there is a squiggle that's labeled "RNA." And
198 1 contribute to enrichment is if a sequence of interest is 2 copied in step 1C and a sequence that is not of interest 3 is not copied in step 1C. But it's not that simple. 4 You could have copying, for example, that doesn't 5 include the adaptor, and then, by the end of this 6 process, you won't have generated, for a given nucleic 7 acid fragment, a sequenceable library. 8 MS. CIPRIANO: Okay. I think it's 9 probably a good time to take a break. 10 (Whereupon, a luncheon recess was taken 11 from 11:38 a.m. to 12:30 p.m.) 12 BY MS. CIPRIANO: 13 Q. Okay. Welcome back, Dr. Sims. I'd like to 14 start talking about the reference that we've been 15 referring to in your papers and in -- in other papers in 16 the case as "Meyer," and that is Exhibit 1006. We'll 17 give you a copy. 18 And just so we're on the same page, do you 19 recognize Exhibit 1006? 20 A. I recognize this Exhibit. 21 Q. And this is the Meyer reference that you 22 discuss in your declaration?	200 1 next to the -- next to the first arrow or across the 2 first arrow that points down are the words "cDNA 3 synthesis and amplification by SMART protocol." 4 Do you see that? 5 A. I see that. 6 Q. So Meyer used a protocol that is a SMART 7 protocol to convert RNA to cDNA; is that accurate? 8 A. The SMART protocol converts RNA into cDNA. 9 Q. You're familiar with the SMART protocol; right? 10 A. I am familiar with the SMART protocol. 11 Q. Have you used the protocol in your research? 12 A. I have used the SMART protocol in my research. 13 Q. And in what capacity have you used the SMART 14 protocol? 15 A. I have used the SMART protocol for single-cell 16 RNA sequencing. 17 Q. So as part of the SMART protocol, one of the 18 steps is that cap primers are added to the ends of mRNA 19 transcripts; is that accurate? 20 A. There are adaptors in the figure labeled "cap 21 primer" in blue. Those adaptors are added by the SMART 22 protocol.

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201 1 Q. So the standard cap primers or adaptors used in 2 the SMART protocol contain, at their 3' end, a sequence 3 complementary to a poly(A) tail; is that right? 4 A. In the SMART protocol, there are two 5 oligonucleotides that contain a cap sequence. One of 6 them is in a primer that also includes poly(T). The 7 other one is in a second oligo that's commonly referred 8 to as a template-switching oligo. 9 Q. So in Meyer's protocol, he did not use the 10 standard oligo from the SMART protocol that contains a 11 primer that includes a poly(T) section; correct? 12 A. Meyer substituted a customized oligonucleotide 13 for the reverse transcription primer that is normally 14 used in the SMART protocol. 15 Q. And Meyer refers to this substitute customized 16 oligonucleotide as his "broken chain T primer," right? 17 A. The reverse transcription primer is referred to 18 as a "broken chain T primer." 19 Q. So the result of Meyer's use of the SMART 20 protocol is he ended up with a mixture of cDNA molecules 21 that are complementary to the mRNA in the original 22 sample and with cap primers on either end; is that	203 1 Q. And Meyer's method included a step after 2 fragmentation where the fragments undergo end repair so 3 that adaptors can be attached; is that accurate? 4 A. The fragments undergo an end repair in the 5 Meyer protocol after fragmentation. 6 Q. So the results of the normalization, 7 fragmentation by sonication or nebulization step 8 reported in Meyer would be a mixture containing many 9 different smaller nucleic acid molecules that are pieces 10 of the cDNA generated from the SMART protocol; correct? 11 A. Those processes result in the generation of 12 smaller pieces of nucleic acid fragments that originate 13 from the cDNA amplicons. 14 Q. And this would include fragments that contain 15 the 5' end, fragments that contain the 3' end and 16 fragments from the internal sequence of the cDNA; is 17 that accurate? 18 A. The fragments include fragments corresponding 19 to the 5' end of the original mRNAs, the internal 20 fragments and fragments that represent the 3' end of the 21 mRNAs. 22 Q. And in the figure in Meyer -- in Additional
202 1 accurate? 2 A. The Meyer protocol results in the production of 3 cDNA that's complimentary to RNA molecules in the 4 original sample, and those cDNA molecules have cap 5 primers on both the 3' and 5' ends. 6 Q. Okay. So then the next step that Meyer 7 portrays in his figure, in the words over the arrow, is 8 "normalization, fragmentation by sonication, or 9 nebulization." Do you see that? 10 A. I see that. 11 Q. Fragmentation, as it's referenced here is the 12 process of breaking the longer cDNA strand into smaller 13 fragments that are easier to sequence; right? 14 A. Fragmentation breaks the cDNA product of 15 reverse transcription into smaller fragments to 16 facilitate sequencing to make it possible to sequence 17 them with, for example, the 454 platform. 18 Q. What is the difference between sonication and 19 nebulization? 20 A. I don't recall the detailed mechanism of 21 nebulization, but sonication uses sound waves to 22 fragment nucleic acids in this context.	204 1 File 4, the 5' end fragments are on the far left of that 2 section with a blue rectangle and a longer white 3 rectangle; right? 4 A. In the arrow after normalization fragmentation 5 by sonication or nebulization, there are four fragments 6 depicted, and the one on the far left with the blue 7 rectangle and the longer white rectangle represents the 8 5' end fragments. 9 Q. And then next to that, slightly to the right of 10 the 5' end fragments, there are two empty white boxes or 11 white rectangles. Those are the inter -- representing 12 the internal fragments; correct? 13 A. Those represent internal fragments. 14 Q. And then on the -- continuing to the right, the 15 far right representation in that area of the figure, 16 there is a -- a bar that has a white section, a green 17 section and a blue section. That represents the 3' 18 fragments; correct? 19 A. The fragment with the white, green, and blue 20 rectangles represents 3' end fragments. 21 Q. So in the next -- the next step in Meyer is 22 labeled "Ligation to pseudo double-stranded adaptors."

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205 1 Do you see that? 2 A. I see that. 3 Q. And in this step, Meyer introduced two adaptors 4 to the mixture to ligate to the available ends of the 5 fragments in the mixture; is that accurate? 6 A. Can you repeat the question? Sorry. Sorry. 7 Q. Mm-hmm. Okay. So in the ligation to pseudo 8 double-stranded adaptors, Meyer introduces two adaptors 9 to the mixture to ligate to the ends that are available 10 for ligation of the fragments in the mixture; is that 11 accurate? 12 A. Meyer introduces two different pseudo 13 double-stranded adaptors for ligation to a subset of the 14 fragments in the mixture. 15 Q. And what subset of fragments are you 16 referring to? 17 A. Fragments that include the 5' phosphate 18 necessary for ligation. 19 Q. And you would agree that all fragments that 20 include a -- the 5' phosphate necessary for ligation 21 would be bound to an adaptor at the end of this 22 reaction; right?	207 1 rectangle with an arrow over it. Do you see that? 2 A. I see that. 3 Q. So that represents a 5' end fragment with a B 4 adaptor attached to it; am I interpreting that 5 correctly? 6 A. That's a 5' end fragment with a B adaptor 7 attached to it. 8 Q. Okay. And then a little bit to the right, 9 there's a rectangle or fragment, a representation that 10 has a blue rectangle, a little white rectangle, and a 11 yellow rectangle with an arrow over it. That's 12 representing a 5' end fragment with an A adaptor 13 attached to it; correct? 14 A. That's a 5' end fragment with an A adaptor 15 attached to it. 16 Q. And then in the middle of the figure in that 17 same section, there's a title that's "Internal 18 Fragments," and there are four permutations of internal 19 fragments: one with two A adaptors; one with two B 20 adaptors, and so the A adaptors in yellow and the B 21 adaptors in red. And then there are two that have one 22 of each of A and B on either end; is that accurate?
206 1 A. The ligation process may not be 100 percent 2 efficient, so it's possible that some of them were not 3 ligated to adaptors. 4 Q. The goal of this step would be to attach 5 adaptors to as many of the fragments as possible; is 6 that fair? 7 A. The goal would be to ligate at least one 8 adaptor to as many of the fragments as possible. There 9 are some fragments for which ligation of two adaptors is 10 less common and not necessary. 11 Q. So if we take the subset of fragments that 12 represent the internal fragments, the goal would be to 13 attach two adaptors to each of those internal fragments 14 as much as possible; is that true? 15 A. One would try to ligate the A and B adaptors to 16 as many of the internal fragments as possible. 17 Q. So I'd like to go through the products that are 18 made in that ligation reaction that Meyer sets forth in 19 his figure. So if we work left to right, we have, under 20 the 5' end fragments, the words that are on the 21 left-hand side of the diagram. There's a fragment that 22 has a blue rectangle, a white rectangle and a red	208 1 A. I agree. 2 Q. And then, if we look at the 3' end fragments, 3 we essentially have the same -- same options as what was 4 on the 5' end. There's one 3' end fragment that's 5 represented as having the B adaptor attached to it, and 6 one 3' end fragment representation that has the A 7 adaptor attached to it; is that accurate? 8 A. I agree. 9 Q. Okay. So after these adaptors are added, the 10 next step that Meyer performs is a PCR reaction with 11 specific primers. Do you understand that? 12 A. The next step in the protocol is a PCR 13 reaction. 14 Q. And Meyer used four primers for that PCR 15 reaction; correct? 16 A. Four primers are used for that PCR reaction. 17 Q. And those -- let me restart. So the primers 18 that Meyer used, he called A, B, A plus half switch, and 19 A plus TRSAC; right? 20 A. I see that. 21 Q. So in the PCR reaction that Meyer ran with 22 these four primers, Meyer indicates that any fragment

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209 1 with two versions of the same adaptor, for example the 2 internal fragments that have two A adaptors or two B 3 adaptors, are suppressed; is that right? 4 A. PCR suppression occurs for fragments that have 5 A adaptors on both ends and fragments that have B 6 adaptors on both ends. 7 Q. And the flip side of that is that all fragments 8 -- wait, let's pause for a second. 9 PCR suppression, what is "PCR suppression"? 10 A. PCR suppression is a class of mechanisms that 11 reduces the efficiency of amplification during a PCR 12 reaction. 13 Q. So essentially, in Meyer's reaction, any 14 fragment that has the same adaptor on both ends will not 15 be exponentially amplified; right? 16 A. The amplification efficiency of the vast 17 majority of fragments with A adaptors on both ends or B 18 adaptors on both ends is expected to be much lower than 19 other fragments in the PCR reaction. 20 Q. And the fragments with different adaptors on 21 either end, meaning one end is an A adaptor and one end 22 is a B adaptor, those will be exponentially amplified;	211 1 correct? 2 MR. HOAGLAND-HANSON: Objection to 3 form. 4 A. The intention is to exponentially amplify 5 fragments with an A adaptor on one end and a B adaptor 6 on the other end, although not all fragments have an A 7 adaptor on one end and a B adaptor on the other end 8 before the reaction starts. Some of the fragments have, 9 for example, an A adaptor inserted during the PCR 10 process. 11 Q. So after the PCR amplification of these 12 fragments, the fragments were sequenced on a 454 13 sequencer; right? 14 A. Sequencing occurred on a 454 sequencer after 15 the amplification process, although there are some 16 intervening steps. 17 Q. And what "intervening steps" are you referring to? 18 A. The PCR product was purified with a QIAGEN kit 19 to remove excess primer, among other contaminants. 20 Excuse me. 21 Q. So I'd like to look at your declaration, to 22 talk a little bit about your interpretations of the
210 1 correct? 2 MR. HOAGLAND-HANSON: Objection to form. 3 A. Most fragments with an A adaptor on one end, a 4 B adaptor on the other end will be exponentially 5 amplified. 6 Q. And are you -- you're using "most" there with 7 the expectation just that all biological mechanisms are 8 imperfect? 9 A. I'm using "most" because this is a complex 10 mixture of nucleic acid sequences with different 11 sequence content, different lengths; amplification 12 efficiencies can vary. 13 Q. Okay. But Meyer's intention, at least as 14 indicated in this figure, he has arrows from the far 15 left 5' end fragment that has an A adaptor and a B 16 adaptor down to "exponential amplification"; he has an 17 arrow from the two internal fragments with an A adaptor 18 and a B adaptor on either end, an arrow to "exponential 19 amplification;" and there's an arrow from the 3' end 20 fragment that has an A and a B adaptor on either end to 21 "exponential amplification." Those groups, his 22 intention is that those will be exponentially amplified;	212 1 protocol in Meyer. So if we could look at paragraph 2 143. In the second sentence, you state: 3 "Among other features, the method 4 described in Meyer was designed to ensure that 5 sequences near the 3' end of mRNA molecules 6 were adequately represented in the final 7 sequencing data, as those regions are sometimes 8 lost to sequencing error." 9 Do you see that? 10 A. I see that. 11 Q. When you say that "those regions are sometimes 12 lost to sequencing error," what do you mean? 13 A. As we discussed earlier, the 454 sequencer in 14 particular struggles to accurately sequence long 15 stretches of homopolymers, and so the authors were 16 concerned that homopolymers -- homopolymer regions 17 greater than 8 base pairs in length would be filtered 18 out of the data. 19 Q. So in the next sentence you -- going back to 20 paragraph 143, in the sentence right after the one that 21 we were just talking about: 22 "The broader full transcriptome

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213 1 sequencing method disclosed in Meyer is also a 2 selective enrichment method as it required 3 selectively enriching for mRNA molecules over 4 other types of RNA and other nucleic acids 5 present in the original sample." 6 Do you see that? 7 A. I see that. 8 Q. The selective enrichment of mRNA over other 9 types of RNA in the sample occurs during the performance 10 of the SMART protocol; right? 11 MR. HOAGLAND-HANSON: Objection. Form. 12 A. The protocol in Additional File 4 states that, 13 at the top, step 1, "RNA Template Preparation": 14 "These steps are recommended but may 15 not be necessary depending on your protocol of 16 choice for isolating total RNA." 17 So depending on how total RNA is 18 isolated, there are some types of RNA species 19 that will be removed. 20 For example, it's common for small 21 RNAs, like microRNAs, to be removed during the 22 process of isolating an RNA sample. The SMART	215 1 during the PCR reaction, which includes a primer that 2 hybridizes to a poly(T) sequence. 3 Q. And where in the protocol are you referring to 4 when you're talking about the "PCR reaction"? 5 A. The PCR reaction includes a primer with a 6 poly(T) tract in it, and so it may disproportionately 7 amplify fragments in the library that have poly(A) 8 tracts. MRNA molecules contain poly(A) tracts. 9 Q. So is it your position that there will be RNA 10 in the cDNA mixture, at that level of the -- let's -- 11 let's step back. 12 In order to enrich the mRNA over other types of 13 RNA, there have to be other types of RNA present in the 14 sample; is that fair? 15 MR. HOAGLAND-HANSON: Objection. Form. 16 A. I just want to clarify that the statement I 17 made earlier about the potential for additional 18 enrichment to occur during the PCR reaction, at that 19 point I don't expect there to be any actual RNA 20 molecules present, but there are DNA molecules that 21 represent those RNA sequences. 22 There could also be, at that stage in the
214 1 protocol also contributes to the selection of 2 polyadenylated mRNA. 3 For example, ribosomal RNA will be less 4 frequently or less efficiently reverse 5 transcribed by the SMART protocol because 6 ribosomal RNAs are not polyadenylated. 7 Q. So the process of selectively enriching for 8 mRNA molecules over other types of RNA, you agree it 9 occurs in that first arrow down of Meyer in the 10 Additional File 4 figure, in the cDNA synthesis step? 11 MR. HOAGLAND-HANSON: Objection. Form. 12 Q. Let me -- let me -- I -- let me rephrase my 13 question, because I feel like I can make it clearer. 14 So the selective enrichment of mRNA molecules 15 over other types of RNA that you are referring to in 16 paragraph 143, happens before fragmentation -- before 17 the fragmentation step that is discussed in Meyer; is 18 that accurate? 19 MR. HOAGLAND-HANSON: Same objection. 20 A. Enrichment for mRNA molecules over other types 21 of RNA, does occur before the fragmentation step, but I 22 wouldn't discount the possibility that it may also occur	216 1 protocol, small amounts of fragments that originated 2 from non-mRNA species. Those could be further depleted 3 by the PCR protocol that's described here because of the 4 inclusion of a primer with a poly(T) tract in it. My 5 expectation is that the authors intend for the majority 6 of the selection process to occur during total RNA 7 isolation and the SMART protocol. 8 Q. So moving to paragraph 144, you state: 9 "In order to selectively enrich for 10 sequences falling near the 3' end of the RNA 11 molecules, Meyer applies special chemistry to 12 these sequences." 13 Do you see that? 14 A. I see that. 15 Q. What are you referring to as "special chemistry"? 16 A. There are many components to this chemistry. A 17 very critical component that I highlight in 18 paragraph 145 is the broken chain poly(T) adaptor 19 sequence that is specifically targeted by a primer 20 containing a sequence complimentary to the broken chain 21 poly(T) adaptor sequence such that fragments containing 22 regions near the poly(A) tail are enriched in the final

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217 1 sequencing library. 2 Q. So we established throughout our discussion 3 that in order for something to be enriched, it must end 4 up with a higher proportion of the enriched element as 5 compared to other elements in the mixture; fair? 6 MR. HOAGLAND-HANSON: Objection. Form. 7 A. My understanding of the term "enrichment" in 8 this context, is a process that results in 9 overrepresentation of sequences of interest in a sample 10 relative to other nucleic acid fragments in the sample. 11 Q. So there always has to be a comparator of some 12 sort, correct, when we're talking about enrichment? 13 MR. HOAGLAND-HANSON: Objection to 14 form. 15 A. To assess enrichment, one would compare the 16 abundance of sequences of interest to that of other 17 sequences in the sample. 18 Q. Okay. So when you say, "in order to 19 selectively enrich for sequences falling near the 3' end 20 of the RNA molecules," what are you comparing that -- 21 those 3' ends to when you're talking about enrichment? 22 A. There are multiple comparisons that could be	219 1 A. Yes, I'm there. 2 Q. So like the method in Additional File 4, the 3 method in Figure 1 uses the SMART protocol to convert 4 mRNA to cDNA; right? 5 A. The method outlined in Figure 1 uses the SMART 6 protocol for cDNA synthesis from mRNA. 7 Q. And then similar to the protocol in Additional 8 File 4 in Figure 1, Meyer fragments the cDNA, but here 9 in Figure 1 only sonication is listed, right? 10 A. I see that Figure 1 describes "fragmentation by 11 sonication," specifically. 12 Q. And in Figure 1, the same types of fragments 13 are generated from that fragmentation as in Additional 14 File 4; correct? 15 A. The same types of fragments are generated in 16 both protocols. 17 Q. And those fragments -- there are going to be 18 some fragments that contain the 5' end, some fragments 19 that are internal and some fragments that are going to 20 contain the 3' end, right? 21 A. 5' end internal and 3' end fragments will be 22 generated by sonication in this protocol.
218 1 drawn to assess enrichment. For example, the Meyer 2 authors compare the number of sequencing reads that 3 contain the broken chain poly(T) adaptor sequence to the 4 total number of reads sequenced to assess enrichment of 5 3' end fragments. 6 One could also compare the frequency of 3' end 7 fragments to the abundance of all of the fragments in a 8 sample, regardless of whether or not those particular 9 fragments are sequenced. 10 Q. So Meyer -- if we look back at Meyer -- we've 11 been talking about the protocol that's in Additional 12 File 4, right? 13 A. We've been discussing the protocol in 14 Additional File 4. 15 Q. Meyer discloses another method that is similar 16 to that method. Do you recall that? 17 A. I recall a method that is outlined in Figure 1 18 of Meyer as well. 19 Q. So if we could turn to Figure 1 in Meyer, which 20 is on page 3 of Exhibit 1006. Are you there? 21 A. I'm there. Oh, sorry, which -- which page? 22 Q. 3.	220 1 Q. In Figure 1, the same A and B adaptors were 2 ligated to the available ends of the fragments, just 3 like it was -- they were ligated to the fragments in 4 Additional File 4; right? 5 A. A and B adaptors are ligated to the three 6 different types of fragments listed, similarly to in 7 Additional File 4. 8 Q. Now, in -- in Figure 1, unlike Additional 9 File 4, only three different primers were used for the 10 PCR reaction; is that accurate? 11 A. The protocol in Figure 1 involves the use of 12 three different primers for PCR. 13 Q. And those primers -- there's a primer 14 complementary to adaptor A that is in -- it's a yellow 15 arrow; correct? 16 A. There's a primer complementary to adaptor A 17 that's a yellow arrow. 18 Q. And there's a primer complementary to adaptor B 19 that is a red arrow; correct? 20 A. I agree. 21 Q. And then there's a primer complementary to the 22 cap primer which is a blue arrow with a yellow tail, if

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221 1 you will? 2 A. There's a primer complementary to the cap 3 that's a blue arrow with a yellow tail. 4 Q. The method of Figure 1 does not use a primer 5 directed to the broken T chain; right? 6 A. The protocol in Figure 1 does not use the 7 broken chain T adaptor primer during PCR. The broken 8 chain poly -- there is a broken chain poly(T) primer 9 used during reverse transcription. 10 Q. And there you're talking about the conversion 11 of RNA to cDNA; correct? 12 A. The reverse transcription reaction to which I 13 referred is the conversion of mRNA to cDNA. 14 MR. HOAGLAND-HANSON: Linnea, we've 15 been going for about an hour. 16 MS. CIPRIANO: Okay. You want to take 17 a break? 18 (Whereupon, a short break was taken.) 19 BY MS. CIPRIANO: 20 Q. So thinking about the sequencing data that is 21 reported in the Meyer reference, that sequencing data 22 was obtained using the method described in Figure 1 of	223 1 larvae, as illustrated in Figure 1, and 2 sequenced using the 454 GS FLX platform." 3 Do you see that? 4 A. I see that. 5 Q. And it says: 6 "This single sequencing run produced 7 628,649 reads with an average sequence length 8 of 232 bases." 9 Do you see that? 10 A. I see that. 11 Q. In the -- in the discussion section that you 12 were talking about, when you were referring to the data 13 at the beginning of the discussion section -- 14 A. Mm-hmm. 15 Q. -- one of the expectations that that -- the 16 data prediction is based on is an "average read length 17 of 232 base pairs." Do you see that? 18 A. I see that. 19 Q. Is it fair to correlate that 232 base pair 20 average to the average sequence length that was the 21 results of the sequencing run prepared after the method 22 of Figure 1?
222 1 the reference. Do you recall that? 2 A. There are multiple references to sequencing 3 data in the Meyer paper. For example, there's a 4 reference to sequencing data in the first paragraph of 5 the discussion which describes the number of raw reads 6 that contain the broken T adaptor, for example. My 7 interpretation is that those data arose from the 8 protocol in Additional File 4. 9 Q. And what's the basis for that interpretation? 10 A. In the Methods section, there is a statement -- 11 let me be specific. In the Methods section on page 14, 12 in the top left corner, there is a statement: 13 "A step-by-step protocol for the 14 library preparation method outlined above is 15 provided in the additional files, accompanying 16 this article (Additional File 4)." 17 Q. So if we look at page 2 of Meyer. Are you 18 there? 19 A. I'm there. 20 Q. Under the "Results" heading, there's a 21 statement in that: 22 "A cDNA sample was prepared from coral	224 1 MR. HOAGLAND-HANSON: Objection. Form. 2 A. Can you clarify what you mean by "is it fair" 3 to compare -- 4 Q. Sure. Yeah. 5 So let's break it down. So you agree that 6 Meyer reports that after he performed the method of 7 Figure 1 and ran a sequencing run, he reported an 8 average sequence length of 232 bases; right? 9 MR. HOAGLAND-HANSON: Objection. Form. 10 A. I see that in the Results section, the paper 11 states, in the second sentence of the Results section: 12 "This single sequencing run produced 13 628,649 reads, with an average sequence length 14 of 232 bases." 15 And I see that 232 bases is the same 16 number of bases in the first paragraph of the 17 discussion. 18 Q. Okay. And the "232 bases," that sequencing run 19 was performed on a sample that had gone through the 20 method of Figure 1; correct? 21 MR. HOAGLAND-HANSON: Objection. Form. 22 A. As I said earlier, my interpretation of the

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225 1 paper, because of the statement in the Methods section, 2 that -- 3 "A step-by-step protocol for the 4 library preparation method outlined above is 5 provided in additional files accompanying this 6 article, Additional File 4." 7 -- that the sequencing data described 8 in the first paragraph of the discussion was 9 generated using the protocol in Additional 10 File 4. 11 I would like to also point out that my 12 opinion about, for example, the anticipation of 13 Claim 1 of the '012 patent by Meyer would not 14 change had the protocol implemented by Meyer to 15 generate those data been the protocol in 16 Figure 1. 17 Q. So if we look at the paragraph that you pointed 18 to at the end -- in the Methods section on page 14. So 19 you referred to the first sentence: 20 "A step-by-step protocol for the 21 library preparation method outlined above is 22 provided in the additional files accompanying	227 1 Do you see that? 2 A. I see that. 3 Q. So is it fair to interpret this as the method 4 that Meyer used to prepare the coral larvae cDNA is 5 different than what is set forth in Additional File 4? 6 A. It's not entirely clear to me what Meyer 7 modifications are referred to in that statement. For 8 example, the cDNA preparation -- or cDNA synthesis step 9 in Additional File 4 uses a different reverse 10 transcriptase than the one described in the Methods 11 section. It's possible that the statement is referring 12 to that minor modification. 13 Q. But you would agree that this statement implies 14 that the method that Meyer used to prepare the coral 15 larvae cDNA was different than the method set forth in 16 Additional File 4? 17 MR. HOAGLAND-HANSON: Objection to form. 18 A. I acknowledge the statement to which you're 19 referring, but the phrase "preparing coral larvae cDNA" 20 could refer to multiple steps. My interpretation is 21 that it refers to cDNA synthesis, and there is a minor 22 modification there, namely a different reverse
226 1 this article, Additional File 4. That protocol 2 includes minor modifications that we have 3 recently developed to reduce the number of 4 manipulations required, improve reproducibility 5 and to further reduce adaptor concatenation." 6 Do you see that? 7 A. I see that. 8 Q. Do you have an understanding of what -- what is 9 meant by "the minor modifications that we have recently 10 developed"? 11 A. I would hesitate to draw a one-to-one 12 comparison between each of the minor modifications 13 listed there and particular steps in the Additional 14 File 4 protocol. 15 Q. In the -- if we look at Additional File 4, so 16 in the first page of Additional File 4, on page 19 of 17 the Exhibit. 18 A. I see that. 19 Q. There's a note that says: 20 "The version of the protocol shown here 21 includes minor modifications from that used for 22 preparing coral larvae cDNA."	228 1 transcriptase enzyme. 2 Q. Let's turn back here to your declaration -- 3 well, let me look at your declaration and then we'll 4 look back at Meyer. 5 So if we look at paragraph 184, and you talk a 6 little bit in paragraph 184 about the -- the data that 7 you were just referring to in the discussion section; 8 right? 9 A. Paragraph 184 refers to the first paragraph of 10 the discussion section to which I was referring. 11 Q. And in the part that you quote from Meyer, 12 there is a statement about the "expectation of about 13 10 percent." Do you see that? 14 A. I see the statement about an "expectation of 15 about 10 percent." 16 Q. And what is your understanding of about how 17 Meyer estimated that 10 percent value? 18 A. My understanding is that Meyer divided 232 base 19 pairs by 2,200 base pairs and arrived at a number that 20 was roughly 0.1, or 10 percent. 21 Q. And where does that 2,200 base pair number come 22 from?

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229 1 A. My interpretation is that the 2,200 base pair 2 size came from running an electrophoretic gel on cDNA 3 amplicons. 4 Q. And that gel on cDNA amplicons was run on the 5 cDNA before Meyer fragments the -- the cDNA transcripts; 6 correct? 7 A. That gel is run prior to fragmentation of 8 the cDNA. 9 Q. Meyer does not report or provide any analysis 10 of the proportion of read fragments that correspond to 11 the 5' end; right? 12 A. I don't recall any specific discussion in Meyer 13 quantifying enrichment of 5' end fragments. 14 Q. And there's no analysis in Meyer about the 15 relative abundances of the fragments before the PCR 16 amplification process; correct? 17 MR. HOAGLAND-HANSON: Objection to 18 form. 19 A. Can you repeat that question? I'm sorry. 20 Q. Mm-hmm. So my question is whether Meyer 21 provides any analysis about the relative abundances of 22 the nucleic acid fragments before the PCR amplification	231 1 have no questions. 2 THE REPORTER: Would you both like a 3 rough draft? 4 MR. HOAGLAND-HANSON: Yes, please. 5 MS. CIPRIANO: Yes, please. 6 (Time Noted: 2:14 p.m.) 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
230 1 process in his method? 2 MR. HOAGLAND-HANSON: Objection. Form. 3 A. So if we're referring to steps after 4 fragmentation but prior to PCR amplification, Meyer does 5 report running a gel on those fragments, which evaluates 6 their relative abundance as a function of length. 7 Q. And from that gel, can you make -- draw any 8 conclusions about what type of fragment they are, the 9 types being that we've talked about; the 5' end, the 10 internal fragments, or the 3' end? 11 A. I would not expect that gel to enable 12 assessment of the 5' end fragments, internal fragments 13 or 3' end fragments independently of each other. 14 They'll be mixed together. 15 MS. CIPRIANO: If we can take a short 16 break. I might be done. 17 MR. HOAGLAND-HANSON: Okay. 18 THE WITNESS: Okay. 19 (Whereupon, a short break was taken.) 20 MS. CIPRIANO: I have no further 21 questions. Thank you very much. 22 MR. HOAGLAND-HANSON: Okay. And we	232 1 A C K N O W L E D G M E N T 2 3 STATE OF NEW YORK) 4 :ss 5 COUNTY OF) 6 7 I, PETER SIMS, hereby certify that I have 8 read the transcript of my testimony taken under oath in 9 my deposition of the 27th day of June, 2025; that the 10 transcript is a true, complete and correct record of my 11 testimony, and that the answers on the record as given 12 by me are true and correct. 13 14 15 _____ 16 PETER SIMS 17 Signed and subscribed to before 18 me, this day 19 of , 2025. 20 21 _____ 22 Notary Public, State of New York

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23 (233 to 236)

233	235
1 CERTIFICATE 2 I, BROOKE E. PERRY, Certified Reporter and Notary 3 Public within and for the State of New York, do hereby 4 certify: 5 That PETER SIMS, Ph.D., the witness whose deposition 6 is hereinbefore set forth, was duly sworn by me before 7 the commencement of such deposition and that such 8 deposition was taken before me and is a true record of 9 the testimony given by such witness. 10 I further certify that the adverse party, TECAN 11 GENOMICS, INC., was represented by counsel at the 12 deposition. 13 I further certify that the deposition of PETER 14 SIMS, Ph.D., occurred at the offices of Williams & 15 Connolly LLP 650 Fifth Avenue, Suite 1500 New York, NY 16 10019 on Friday, June 27, 2025, commencing at 17 8:54 a.m. to 2:14 p.m. 18 I further certify that I am not related to any 19 of the parties to this action by blood or marriage, 20 I am not employed by or an attorney to any of the 21 parties to this action, and that I am in no way 22 interested, financially or otherwise, in the outcome of this matter. IN WITNESS WHEREOF, I have hereunto set my hand this 2nd day of July, 2025. <i>Brooke E. Perry</i> BROOKE E. PERRY	1 _____ 2 (NOTARY PUBLIC) MY COMMISSION EXPIRES: 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
234 1 ERRATA SHEET 2 CASE NAME: INTEGRATED DNA TECHNOLOGIES, INC. V. 3 TECAN GENOMICS, INC. 4 DATE OF DEPOSITION: June 27, 2025 5 WITNESS'S NAME: PETER SIMS, Ph.D. 6 PAGE LINE (S) CHANGE REASON 7 _____ 8 _____ 9 _____ 10 _____ 11 _____ 12 _____ 13 _____ 14 _____ 15 _____ 16 _____ 17 _____ 18 19 20 PETER SIMS, Ph.D. 21 SUBSCRIBED AND SWORN TO BEFORE ME 22 THIS ____ DAY OF _____, 20__.	

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