

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TWINSTRAND BIOSCIENCES, INC.,
Petitioner,

v.

GUARDANT HEALTH, INC.,
Patent Owner.

IPR2022-01400
Patent 11,149,306 B2

Record of Oral Hearing
Held: November 17, 2023

Before SUSAN L. C. MITCHELL, TINA E. HULSE, and
MICHAEL A. VALEK, *Administrative Patent Judges*.

IPR2022-01400
Patent 11,149,306 B2

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The above-entitled matter came on for hearing at 2:00 PM EDT on Friday, November 17, 2023, at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, Virginia.

P R O C E E D I N G S

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JUDGE MITCHELL: Good afternoon everyone, please be seated. So we have a final hearing this afternoon in IPR2022-01400. I'm Judge Mitchell, and with me by video conference are Judges Valek and Hulse. So I would like to get appearances for the parties on the record. So who do I have for Petitioner, and I do know we have a LEAP presenter too, which is great.

MR. HOLMAN: Good afternoon, Your Honors. David Holman from Sterne Kessler Goldstein & Fox on behalf of the Petitioner Twinstrand. With me here today are Tyler Liu from Sterne Kessler and Ralph Powers, who is lead counsel for Petitioner, also from Sterne Kessler.

JUDGE MITCHELL: Great, thank you, and welcome. And for Patent Owner?

MR. ROSATO: Good afternoon, Your Honor, Mike Rosato on behalf of Patent Owner. And I have with me at the counsel table Sonja Gerrard.

JUDGE MITCHELL: Thank you. So as set forth in our oral hearing order, each side has 60 minutes to present its case, but Petitioner has an additional 15 minutes for its LEAP participant. My colleagues and I will certainly do our best to keep track of time, and we have the timer, but you may certainly do the same for yourselves.

Petitioner will present its arguments first as it bears the burden of showing unpatentability of the challenged claims. So Petitioner, would you like to reserve any time for rebuttal?

MR. HOLMAN: Yes, Your Honor, Petitioner would like to reserve 20 minutes for rebuttal, please.

1 JUDGE MITCHELL: Thank you. And Patent Owner, you will have
2 the last word, so would you like to reserve any of your time for rebuttal?

3 MR. ROSATO: Yes, thank you, Your Honor, 15 minutes, please.

4 JUDGE MITCHELL: Thank you. So just one last word before we
5 get into all that, I'll tell you all this, and I know you know it, but to assist
6 Judges Valek and Hulse to follow along with your argument, we do have the
7 demonstratives. If you could just make sure that you identify the slide
8 number if you are on the demonstratives, and that also helps us because we
9 certainly look at the record after the hearing, it helps us to, you know,
10 understand what people are talking about. So, with that said, Petitioner, you
11 may begin when you're ready.

12 MR. HOLMAN: Judge Mitchell, we do have hard copies of the
13 demonstratives --

14 JUDGE MITCHELL: Oh, yes.

15 MR. HOLMAN: Permission for us to use them.

16 JUDGE MITCHELL: Yes, please. Thank you. When you're ready.

17 MR. HOLMAN: May it please the Board, good afternoon. I'm
18 David Holman from Sterne Kessler Goldstein & Fox on behalf of Petitioner
19 Twinstrand.

20 This IPR, of course, concerns Guardant Health's 306 Patent. And at
21 issue before the Board is whether Petitioner has established by a
22 preponderance of the evidence that Claims 1 through 29 of the 306 Patent
23 would have been obvious over certain combinations of the prior art.

24 So today I'll address the elements of the 306 Patent's claimed
25 methods, with particular focus on Claim 1. And I'll discuss what a person of
26 ordinary skill in the art, or a POSA, would have understood these claim

1 elements to mean. I'll discuss combinations of prior art that were set forth in
2 the Petition and how the asserted art discloses the elements of the challenged
3 claims. I'll also address POSA's reasons to combine the art, reasonable
4 expectation of success.

5 Now Patent Owner of course disputes whether certain claim elements
6 are disclosed in the prior art, as well as reasons to combine the prior art
7 references. So I'll be sure to address these issues of dispute too.

8 Let's begin by taking a look at the language of Claim 1 of the 306
9 Patent. This is presented on Petitioner's Slide 4. So, as you can see from
10 the language of Claim 1, it begins with a "method" and then there's five
11 steps, A through E. And I'll address each of these steps in detail shortly.
12 But generally you can see that the method of Claim 1 begins with the step of
13 A, Step A providing a population of cell-free DNA molecules. Step B is
14 tagging those cell-free DNA molecules, we'll spend some time on that
15 element today. Step C is amplifying the tagged molecules, Step D recites
16 sequencing those amplified molecules. And then Step E recites reducing or
17 tracking redundancy for those sequenced molecules. And we'll spend some
18 time on that element as well of course.

19 And briefly if you can just turn to Slide 6, we have a short summary, a
20 refresher, of the grounds that were set forth in the Petition. The Petition's
21 primary combination of art includes the Schmitt patent application
22 publication and then the Narayan reference. And that combination of
23 Schmitt and Narayan form the basis for Ground 1, as well as the underlying
24 basis for Grounds 2, 3, and 4 where we included the Meyer, Craig, and
25 Kivioja references respectively. Today I'll primarily focus on the

1 combination Ground 1, the Schmitt and Narayan combination. And again,
2 using Claim 1 for our talking points.

3 So with that backdrop, let's dive into Claim 1's method. Claim 1
4 begins with Step A, which is providing a population of cell-free DNA
5 molecules. This is shown on Petitioner's Slide 8. Now this element of
6 Claim 1 really isn't disputed very much between the parties, so this will be
7 just a brief refresher that Claim 1(A) recites providing its population of cell-
8 free DNA molecules that have first and second complementary strands. As
9 the Petition showed, the Narayan reference teaches applications of
10 sequencing cell-free DNA molecules, having first and second
11 complementary strands. The cell-free DNA molecules were isolated from
12 human blood samples. The Petition also noted that the Schmitt reference
13 refers to sequencing nucleic acids serum biomarkers.

14 So that brings us to Step B, the tagging step. If you can turn to Slide
15 10 we have the language of Step B here. So as you can see from the
16 highlighted text in this slide, Claim 1 recites this tagging step where it's
17 tagging a plurality of the cell-free DNA molecules in the population with
18 duplex tags comprising molecular barcodes.

19 And this tagging process, according to the claim, it produces tagged
20 parent polynucleotides that have duplex tags attached to both ends of the
21 molecule, both ends of the cell-free DNA molecule. And as the tagging step
22 goes on, there's a wherein clause that refers to the number of different
23 barcode combinations, which I definitely will address shortly. But first I'd
24 like to focus on this highlighted portion of the claim which uses this phrase,
25 duplex tags comprising molecular barcodes.

1 Patent Owner argues that Schmitt's 3-mer hybrid tag embodiment
2 does not constitute duplex tag comprising molecular barcodes because in
3 Schmitt's methods this 3-mer barcode is used in combination with the DNA
4 fragment ends to practice Schmitt's duplex sequencing methods. But as the
5 Petitioner has established, and as I'm going to show you over these next
6 several slides, Schmitt's 3-mer hybrid tag does meet the Claim 1 B's tagging
7 limitation. When you consider the 306 Patent's claim language, the 306
8 Patent's own description of what duplex tags and molecular barcodes are,
9 and the 306 Patent's own hybrid tagging provides.

10 So let's take a look. First let's take a look at what it means to have a
11 molecular barcode. You can turn to Petitioner's Slide 15, please. On the
12 left box is testimony from Petitioner's witness, Dr. Spellman, describing
13 molecular barcodes. And you can see the highlighted text at the bottom. Dr.
14 Spellman says that barcodes, the molecular barcodes or tags that are used to
15 "label and track individual molecules." Now the Petition similarly states at
16 Page 3 that molecular barcodes are nucleotide sequences that help to further
17 identify and distinguish the sequence DNA fragments from one another.
18 Again, that's Petition, Page 3.

19 And this description of what a molecular barcode is, is consistent with
20 how the 306 Patent itself characterizes molecular barcodes. And you can see
21 that in the box on the right where the patent refers to molecular barcodes,
22 that they're used to differentiate polynucleotides in the sample. And I'll
23 note that according to the 306 Patent, a molecular barcode can indeed be a
24 3-mer. That's at Column 23, Lines 12 to 16.

1 So now we have this molecular barcode, but of course the claimed
2 tagging recites duplex tags comprising molecular barcodes. So let's take a
3 look at what it means to have a duplex tag.

4 We turn to Petitioner's Slide 12, please. So on Slide 12 I'll direct
5 your attention to the box at the bottom left. And that is where you can see
6 the 306 Patent's description of a duplex tag. The 306 Patent defines duplex
7 tags as tags that "differently label the complementary strands (i.e. the
8 'Watson' and 'Crick' strands) of a double-stranded molecule." And that's at
9 the 306 Patent, Exhibit 1001, Column 17, Lines 9 through 13. And the
10 Petition expressly referred to this definition, Page 27, cites the very same
11 passage in the 306 Patent. Dr. Spellman also refers to the same definition in
12 his declaration, that's Exhibit 1002, Paragraph 162.

13 So in Claim 1 we have these duplex tags, which are tags that
14 differently label the complementary strands of a double-stranded molecule.
15 And these duplex tags comprise molecular barcodes which label and track
16 the individual molecules. And as I mentioned, the 306 Patent says that a
17 molecular barcode can be a 3-mer.

18 Now we line that up with what's taught in the Schmitt reference. If
19 you could turn to Slide 16, please. Our Petition showed that Schmitt's 3-mer
20 tag in this hybrid tag embodiment is a duplex tag comprising molecular
21 barcodes according to the 306 Patent. So as you can see in the example
22 citations here on the slide, the top left box is some language from the
23 Petition that directly refers to the short 3-mer tags, which are labeled as X
24 and Y in Dr. Spellman's figure, refers to these short 3-mers as molecular
25 barcodes. Dr. Spellman does the same. You can see this example on
26 Paragraph 89 of his declaration where he refers to the short n-mer molecular

1 barcodes labeled X and Y. And then it's also evident in Dr. Spellman's
2 figure where he labels the short n-mer barcodes as X and Y, and you can see
3 in the highlighted portion of this figure at the bottom there where he says,
4 where he refers to them as molecular barcodes. And this labeling, this
5 nomenclature, is consistent with what the 306 patent's description of what a
6 molecular barcode is, it's a tag that's used to differentiate polynucleotides in
7 the sample, is consistent with the patent's acknowledgement that molecular
8 barcodes can be a 3-mer. It's consistent with the patent's description of
9 what a duplex tag is. It's a tag, that differently labels complementary
10 strands.

11 Now on the bottom of this slide, bottom box here, you can see some
12 language from the Schmitt reference. Where Schmitt describes using the
13 short n-mer tags in combination with the sheared ends of the DNA fragment
14 to serve as what Schmitt refers to as unique molecular identifiers.

15 Now Patent Owner argues that Schmitt's hybrid method here,
16 combining the 3-mer tag, 3-mer barcode with the fragment ends to serve as
17 unique molecular identifiers in the Schmitt's workflow means that the 3-mer
18 tag cannot be a molecular barcode.

19 But Patent Owner's argument is contradicted by the 306 Patent's own
20 disclosures. In other words, this use of the 3-mer tag, it's in Schmitt's
21 hybrid method, that use, combining it with fragmented ends, does not negate
22 the structure that it is, the structure that meets the 306 Patent's criteria for a
23 duplex tag comprising a molecular barcode.

24 In other words, Schmitt teaches a POSA to make this adaptor
25 comprising a 3-mer tag. And that adaptor with a 3-mer tag, that structure,

1 meets the criteria for the 306 Patent's duplex tag comprising molecular
2 barcodes.

3 And the end result here --

4 JUDGE VALEK: Counsel, let me interrupt you for just a moment. I
5 want to make sure I understand your position. So I'm looking at your Slide
6 12 and the figure from Dr. Spellman's Declaration in Paragraph 89. You're
7 saying that the n-mer, what's labeled I guess X and Y, that's the molecular
8 barcode in Claim 1, correct?

9 MR. HOLMAN: That's correct, Your Honor. The n-mer, which is
10 labeled X and Y, meets the criteria for molecular barcode as claimed in
11 Claim 1.

12 JUDGE VALEK: And so, is it the combination of that 3-mer and the
13 end of the DNA that's the duplex tag in the claim? Is that your position?

14 MR. HOLMAN: Well Schmitt uses the combination of the 3-mer and
15 the end of the DNA in its duplex sequencing methods. But the duplex tag
16 here is a tag that differently labels the complementary strands. And so that
17 is the Y shaped adaptor and the 3-mer, the 3-mer portion attached to the
18 DNA ends.

19 JUDGE VALEK: Okay. So in your diagram, what part is the duplex
20 tag?

21 MR. HOLMAN: It's the Y shaped adaptor, which are the green and
22 purple arms there leading up to the n-mer tag, which is either X or Y,
23 depending on which side of the molecule you're looking at, and then there's
24 a very small fixed sequence yellow portion there, and that's the end of the
25 tag there, the end of the adaptor. And that is the duplex tag as it attaches to
26 the ends of the DNA molecule.

1 JUDGE VALEK: So L and R, the ends that target DNA, are not part
2 of the duplex tag, in your view, correct?

3 MR. HOLMAN: That's correct, Your Honor. Schmitt does say to
4 use the L and R and its hybrid method for distinguishing the strands, but as
5 far as the criteria for a duplex tag, that does not include the L and R.

6 JUDGE VALEK: So the L and R are used to help identify the
7 fragment but they're not part of the duplex tag itself?

8 MR. HOLMAN: That's correct, Your Honor.

9 JUDGE VALEK: You can continue.

10 MR. HOLMAN: Thank you. So after Schmitt teaches to add these
11 tags to the DNA molecules, the end result here is a tagged polynucleotide.
12 So for example if you could turn back to Slide 12, the language of the claim
13 says after tagging, is to produce a tagged polynucleotide wherein the duplex
14 tags are attached to both ends of the molecule. And that's exactly what we
15 see here, and this is directly on point with the question Judge Valek was
16 getting at, is the ends of the molecule, they have the duplex tag. These tags
17 differently label the complementary strand and meet the criteria for duplex
18 tags. And these tags comprise a molecular barcode. This 3-mer tag, which
19 satisfies the mark of the barcode according to the 306 Patent's description,
20 the molecular barcodes.

21 Moreover, all this disclosure in Schmitt is all buttressed by the 306
22 Patent's admissions that hybrid tagging, just like Schmitt's, is fully
23 encompassed within its claimed methods. If we can turn to Slide 18, we
24 have some examples of this.

25 So you can see here on this slide, the top three boxes are all
26 disclosures from the 306 Patent where it refers to identifying

1 polynucleotides by the combination of a DNA barcode and one or more
2 endogenous sequences. That's a DNA barcode and the fragment ends.
3 Additionally it refers to the combination of identifying a combination of
4 DNA barcodes and about ten base pairs of the endogenous sequence. And
5 as you can see, comparing that with the disclosures in Schmitt, which is at
6 the bottom, referring to Schmitt's hybrid method, this is precisely the same
7 method that's taught in Schmitt. So Patent Owner's arguments here that
8 Schmitt's 3-mer tag is not a duplex tag comprising likely a barcode, is belied
9 by the 306 Patent's own disclosures.

10 If you could turn to Slide 14, please, I'd like to address some of that in
11 Patent Owner's arguments here. So on Slide 14 on the bottom left, you can
12 see an excerpt from Schmitt's Figure 1. This figure depicts an embodiment
13 in Schmitt where the alpha and beta SMI, or Single Molecule Identifier
14 sequences, are part of the adaptors which are then attached to the ends of the
15 DNA molecule.

16 In a deposition, Patent Owner's counsel asked Petitioner's expert, Dr.
17 Spellman, about this figure. Dr. Spellman explained that in this figure the
18 alpha and beta SMI tags function as molecular barcodes in Schmitt's duplex
19 sequencing methods. And of course on the right of this, to the right of that
20 figure is Dr. Spellman's figure depicting Schmitt's hybrid tag embodiment,
21 which uses the combination of the 3-mer barcode and the DNA fragments to
22 serve as unique molecular identifiers. But as I mentioned earlier, Schmitt's
23 use of this 3-mer hybrid tag here does not negate the fact that the 3-mer
24 itself, the structure of this 3-mer tag itself, meets the 306 Patent's criteria for
25 duplex tag comprising molecular barcode.

1 Because as we've seen, Schmitt's adaptor has a 3-mer barcode. And
2 the patent says the molecular barcode can be a 3-mer. Schmitt has duplex
3 tags here because it differently labels the complementary strands of the DNA
4 molecule, and the 306 Patent, as we saw, says hybrid tag and its encompass
5 lends methods.

6 So in view of this, the patent's claim language, the disclosures, and
7 the specification, and Schmitt's teachings, a POSA would have indeed
8 understood Schmitt's 3-mer hybrid tag embodiment constitutes a duplex tag
9 comprising a molecular barcode as recited in Claim 1.

10 Now the other aspect of Claim 1 is this number of different
11 combinations of molecular barcodes. So let's take a look at that. That's on
12 Petitioner's Slide 19, please.

13 JUDGE VALEK: Counsel, before you move on, I have another
14 question.

15 MR. HOLMAN: Sure.

16 JUDGE VALEK: I'm looking at Page 27 of the Petition, and this is
17 the section addressing Limitation 1B. And at the bottom of the page there,
18 the last sentence, you seem to say that the Schmitt's hybrid tag embodiment
19 comprises molecular barcodes because the duplex tags comprise both the
20 fragment DNA end sequences and the shorter n-mer tag. Isn't that a
21 statement that at least in the Petition, you contend that the duplex tag is the
22 3-mer plus the end sequence.

23 MR. HOLMAN: Well that's --

24 JUDGE VALEK: Just let me finish up, I'll go on. Are you taking a
25 different position now because what I understood earlier was you were

1 saying it was just the 3-mer plus the adaptor and that little yellow fixed
2 sequence that constituted the duplex tag?

3 MR. HOLMAN: Yeah. Thanks for that question, Your Honor. So
4 the Schmitt's method does use this combination of the n-mer and the
5 fragment ends. And that combination, which is a unique molecular
6 identifier, can be a molecular barcode because it is a barcode that is used to
7 track individual molecules. But our point here is that that use of the 3-mer
8 plus the fragment ends as a unique molecular identifier, does not take away
9 from the fact that the 3-mer itself is also a molecular barcode in the eyes of
10 the 306 patent. So we're definitely not arguing anything new here, it's just a
11 little distinct, a little nuance in the combination of the n-mer and the
12 fragment ends in Schmitt's method is used to track strands, but that doesn't
13 take away from the fact that the 3-mer by itself is still a molecular barcode,
14 meeting the criteria for Claim 1's tagging Step B.

15 If you could turn to Slide 19, please. I'd like to address the number of
16 different combinations of barcodes in Claim 1. The Petition showed POSA
17 would have understood that Schmitt's 3-mer tag meets this limitation. And I
18 have a highlighted text here on the screen, and you can see briefly that it
19 recites that after the tagging with the duplex tags, the cell-free DNA
20 molecules are tagged with n different combinations of molecular barcodes.
21 Where "n" is at least two, and no more than $100,000 \cdot z$. And then the claim
22 goes on to say that "z" is a mean of an expected number of duplicate
23 molecules in the population.

24 On Slide 20 we show that as the Petition argued, the Schmitt's 3-mer
25 hybrid tag that we've been discussing today, meets this claim limitation.
26 Because referring to Schmitt's 3-mer tags, using those as the different

1 combinations of barcodes, results in 4,096 different combinations of
2 molecular barcodes.

3 Now this calculation, referring to the n-mer, is consistent with the way
4 that the 306 Patent characterizes the number of different combinations of
5 molecular barcodes. For example, the 306 Patent says that its methods can
6 use 64 different identifiers. That's at Exhibit 1001, Column 20, Lines 50 to
7 54. Additionally in the 306 patent's example one it refers to a set of eight
8 barcodes and says that that amounts to 64 combinations. So again, it's
9 referring to the combinations of n-mers, not the combination of n-mers plus
10 fragment ends. That's in Column 54, Lines 5 through 15. So the number of
11 combinations of molecular barcodes is based on the n-mer barcodes, not the
12 n-mer plus the fragment ends.

13 And as Dr. Spellman explains, when using Schmitt's 3-mer hybrid tag
14 embodiment, it ultimately doesn't matter whether "z" is 1 or 10 or 100 or
15 800. And this is shown on Slide 21. Schmitt's 4,096 different combinations
16 of molecular barcodes would fall within the claimed range. And this is
17 precisely what's taught in Schmitt and how the Petition presented Schmitt's
18 hybrid tagged embodiment.

19 So moving on, I'd like to briefly address Steps 1C and 1D. If you
20 could turn to Slide 23, please. On the top left you can see the claim
21 language from Claim 1, so we've gone through Step B, which was tagging.
22 And so now Step C is amplifying the tagged polynucleotides. And Step D
23 recites sequencing these amplified molecules.

24 And much like Step A in Claim 1, for Steps C and D there's really not
25 much dispute here between the parties. As you can see in the box on the
26 bottom left, that's a disclosure from Schmitt, where Schmitt refers to or

1 describes amplifying the tagged molecules and sequencing them. And this is
2 also evident from Schmidt's Figure 1, for example, where it refers to PCR,
3 which is amplifying the tagged molecules, and then further down the
4 workflow there's a sequence to the step.

5 So that's going to bring us to Step 1E, the reducing or tracking
6 redundancy step. If you could turn to Slide 25, please. As you can see in
7 the claim language on the left, Step E, Claim 1, is long, it's lengthy and
8 wordy. But generally you can see that the claim has three primary
9 components, or three aspects.

10 It begins with reducing or tracking redundancy of sequence , so I'll
11 definitely address that issue. And then in the middle there's a reference to
12 determining distinct cell-free DNA molecules. And that's based on (i)
13 paired reads, or (i) unpaired reads. And then the third aspect of Step 1E is
14 the wherein clause at the end which refers to mapping sequence reads to a
15 reference sequence.

16 Again, I'm going to address each of these aspects of Step 1E. But I
17 think it's important to first understand what the patent means when it says
18 reducing or tracking redundancy.

19 On the right you can see exemplary disclosures from the 306 Patent
20 saying that reducing or tracking redundancy is achieved by generating
21 consensus sequence reads. At the top portion you can see it says
22 determining consensus sequence reads such as by reducing or tracking
23 redundancy. And it also says reducing redundancy comprises collapsing the
24 sequence reads. And at the bottom again it refers to reducing or tracking
25 redundancy to determine consensus reads.

1 So there's really no question that in the eyes of the 306 Patent,
2 reducing or tracking redundancy of sequence reads is achieved by generating
3 a consensus sequence read.

4 When we look at the prior art on Slide 26, there's no question that
5 Schmitt discloses reducing or tracking redundancy to generate consensus
6 sequence reads. For example in the top box this is an exemplary disclosure
7 from Schmitt, Paragraph 60 where Schmitt refers to this enumerated
8 workflow summary. You see in the highlighted text there Schmitt discloses
9 collapsing the reads to SMI consensus reads. And, in fact, this is one of
10 Patent Owner's primary arguments here, is that Schmitt only discloses
11 collapsing reads in a consensus reads, and Schmitt doesn't do anything with
12 what the petition refers to as raw sequence reads.

13 Which brings us to one of Patent Owner's key arguments here
14 regarding the mapping step. If you'll turn to Slide 27, please.

15 JUDGE VALEK: Counsel, before you move on I have a question
16 about that because I'm not sure I understand the math behind how you
17 collapse a set of reads into a consensus. Is it the case that, the consensus
18 sequence that you get will have, let me rephrase that. Is it the case that there
19 will be at least a subset of the raw sequence reads that will correspond to the
20 consensus sequence?

21 MR. HOLMAN: Yes. So the raw sequence reads will be aligning
22 groups to collapse into a consensus sequence. So the sequence reads are
23 going to be different fragments with different sequences along the target
24 region and so you have this pool of raw sequence readings, some of those
25 will line up that you can collapse into the first step of Schmitt, it's a single
26 strand consensus sequence read. And then once those are made, in Schmitt,

1 the next step in Schmitt's methods refer to collapsing the single strand
2 consensus reads that have partner pairs into a duplex consensus sequence
3 read.

4 Does that answer your question, Judge Valek?

5 JUDGE VALEK: Yeah. You were explaining in the context of
6 Schmitt's DCS methodology, but I'm just talking about collapsing more
7 generally because I think the 306 Patent specification discusses it a little bit
8 more generally. I'm trying to figure out what the difference between the
9 consensus sequence read and the raw reads is.

10 MR. HOLMAN: Well so consensus sequence reads are built from
11 raw sequence reads. So they are, you know, Petitioner's position, it's not,
12 we're not saying they are the same entity, they are two different things.
13 Consensus sequences are made from raw sequence reads. But Petitioner's
14 argument here is that based on the way the patent describes its methods and
15 that the collapsing step can take place before or after mapping; the 306
16 patent also refers generally to just reads or consensus reads more basically
17 based on these disclosures in the patent. That's why Petitioner set forth the
18 argument that the term "sequence reads" in Claim 1, the way it's used in the
19 mapping step, encompasses mapping the consensus sequence reads and
20 mapping the raw sequence reads.

21 JUDGE HULSE: Counsel, I have a question also. Would a person of
22 ordinary skill in the art understand that you could conduct this reducing or
23 tracking redundancy step in Schmitt using only the 3-mer, or does it require
24 the sheared end sequence as well?

25 MR. HOLMAN: So a person of ordinary skill in the art would
26 understand that reducing, if they were practicing Schmitt's hybrid tag

1 method, with the 3-mer hybrid tag, that they would use the 3-mer and with
2 pure fragment ends in reducing your tracking redundancy process. Because
3 that's the way Schmitt's hybrid tag method works, that's the way the 306
4 Patent's hybrid tag method works as well.

5 JUDGE VALEK: I don't mean to interrupt, but I want to follow up.
6 And that's because you need the combination of the sheared end and the 3-
7 mer to uniquely identify the different fragments?

8 MR. HOLMAN: That's correct. With the hybrid tag method, Schmitt
9 says complying with 3-mer with the sheared ends as the unique molecular
10 identifiers. That's right.

11 So if we could refer back --

12 JUDGE HULSE: I'm sorry, sorry, one more on this. So then, why
13 wouldn't it be that the 3-mer and the sheared end constitutes a duplex tag,
14 the molecular barcode of the claims?

15 MR. HOLMAN: Well so the 3-mer combined with the fragment ends
16 is certainly used as a molecular barcode in Schmitt's methods. We're not
17 denying that or disputing that. But the 3-mer itself is also a molecular
18 barcode because Schmitt uses it in this process of identifying the strands.
19 It's not just, this embodiment isn't just using the shear ends, it uses the
20 3-mer molecular barcode and then just combines it with the fragment ends.
21 So it's similar to how some of the other tagging methods work in the 306
22 Patent where it uses a barcode from the left adaptor and a barcode from the
23 right adaptor and the workflow combines those two barcodes, that's the tag
24 it uses to identify the strands. So it's still even 306 Patent's workload
25 combines barcodes. And so it's akin to the same principle where Schmitt
26 says combine this barcode with the fragment end, they're both, you know,

1 the 3-mer is considered a molecular barcode and this combination is used as
2 a molecular barcode in this workflow.

3 JUDGE VALEK: And so in Petitioner's view the term "molecular
4 barcode," whatever that thing is, that molecular barcode, does not need to
5 uniquely identify the fragment all by itself?

6 MR. HOLMAN: That's correct, Your Honor. The molecular
7 barcode, as long as it's used in the process for identify the molecules, it can
8 be combined with another known molecule. It doesn't have to be solely
9 based on that molecular barcode tag.

10 JUDGE VALEK: And so to follow up, when the specification of 306
11 Patent says that a duplex tag is just something that differently labels the
12 fragments, you're saying that differently labeled doesn't mean uniquely
13 labeled?

14 MR. HOLMAN: That's correct, Your Honor. Differently labeled
15 means that you can distinguish the top fragment from the bottom fragment,
16 the top strand from the bottom strand. And it says that, and if you look at
17 the definition of duplex tag, it does say differently labeled complementary
18 strands of A, double stranded molecules. So that's just looking at one
19 molecule, double stranded, you can tell the difference if you label the top
20 strand differently from the bottom strand, that's a duplex tag. And in
21 Schmitt's 3-mer the adaptor, the adaptor 3-mer tag means that definition.
22 Regardless of the fact that Schmitt says now combine that 3-mer with the
23 fragment ends when you're reducing, collapsing, grouping and sorting and
24 things like that.

1 JUDGE HULSE: I'm sorry I'm harping on this. So then did you say
2 then that the molecular barcode has to be able to be uniquely identify the
3 polynucleotide?

4 MR. HOLMAN: The molecular barcode is a tag that labels and tracks
5 molecules. So whether it has to be able to uniquely identify every
6 polynucleotide in the sample, that's not part of the definition of a molecular
7 barcode as Dr. Spellman described and that is characterized in the 306
8 Patent. But as long as it's used -- I'm sorry.

9 JUDGE HULSE: No, no, go ahead.

10 MR. HOLMAN: I was just going to explain that as long as that
11 barcode, that molecular barcode is used in this process of identifying,
12 labeling, and tracking individual molecules, then that's used as a molecular
13 barcode. Which is of course different from like an index barcode where it's
14 used to track sample sources.

15 JUDGE HULSE: Okay. So then the claim says that duplex tags
16 comprising molecular barcodes, that doesn't necessarily mean that those
17 duplex tags have to uniquely identify the polynucleotides, is that what
18 you're saying?

19 MR. HOLMAN: That's correct, Your Honor.

20 JUDGE HULSE: Thank you.

21 MR. HOLMAN: Okay. So referring back to Claim 1's mapping step,
22 Claim 1E, mapping. If you could turn to Slide 27, please. On the left again
23 we have the language from Claim 1, and the mapping step is highlighted at
24 the bottom. And just to remind the Board, the step begins with wherein
25 reducing or tracking with the redundancy of the plurality of sequence reads

1 comprises mapping at least a subset of the plurality of sequence reads to the
2 reference sequence.

3 So this open language is comprising means that somewhere in this
4 reducing or tracking redundancy process, somewhere in there there's a
5 mapping step. Patent Owner's argument here as you can see on the right, at
6 least in example snapshot from the Patent Owner's argument, is that the
7 Petition only points to Schmitt's mapping or consensus sequence reads. And
8 that Claim 1 is limited to mapping the raw sequence reads. That's not quite
9 correct. The Petition pointed to Schmitt's mapping of consensus sequence
10 reads, you saw that earlier on Slide 26, but the Petition also pointed to
11 Schmitt's mapping of raw sequence reads. And the Petition argued that both
12 processes satisfy Claim 1's mapping limitation.

13 So even if Claim 1 were interpreted as more narrowly under the Patent
14 Owner's view that it's limited to mapping raw sequence reads, Schmitt still
15 teaches this limitation.

16 JUDGE VALEK: Counsel, let me ask you a question about that.
17 What about the Patent Owner's argument that the Schmitt's reference to
18 mapping raw sequence reads is not referring to DCS, but rather its referring
19 to kind of the control in Schmitt's experiment as opposed to the actual DCS
20 methodology which you say is what one of skill in the art would combine
21 with Narayan.

22 MR. HOLMAN: Yeah. I'm glad you brought that up, Judge Valek,
23 because that's again and again and again Schmitt uses that mapping of raw
24 sequence reads as part of its workflow. Whether it's a QA/QC step or not,
25 Schmitt consistently using this process of mapping the raw sequence reads
26 built into the duplex sequencing workflow. So this is in Schmitt, just for

1 your reference, this is in Schmitt, which is Exhibit 1083. In Paragraph 66
2 Schmitt refers to, describes mapping raw sequence reads and scoring the
3 mutations. Then of course the workflow goes on, Paragraph 67, 68, to
4 collapse the reads in the single strand consensus sequence reads and duplex
5 consensus sequence reads.

6 Schmit does this again in the PCT exhibit, which is Exhibit 1009, you
7 can look in Example 4, Paragraphs 125 and 128. Those are a totally
8 completely different experiments and Schmitt does it again. He maps the
9 raw consensus reads first, does an initial check, initial mutation check, then
10 moves on to collapsing into single strand consensus and collapsing into
11 duplex consensus reads.

12 So Patent Owner's argument that this mapping of raw sequence reads
13 is prior art, or is a prior art method, it's not very good, is really misplaced
14 here because Schmitt does teach this and it's part of Schmitt's workflow
15 here.

16 JUDGE VALEK: Counsel, I have a question about the two Schmitt
17 references. It seems like the Petition mostly cites Exhibit 1083 whereas the
18 Reply mostly cites Exhibit 1009. Are there differences in the disclosure that
19 Schmitt provides in those two exhibits, and if so, what are those differences?
20 Because I'll admit I'm a little confused by your vacillation back and forth
21 between your citations to those, both of which you refer to as Schmitt.

22 MR. HOLMAN: So there are some differences between the
23 provisional at 1089 and the PCT, which is Exhibit 1009. PCT by itself is
24 prior art to the 306 Patent based on its filing date and publication date. But
25 we run into caution, the Petition referred primarily to the provisional

1 document, Exhibit 1083 to convey that the disclosures in the provisional
2 carried forward into the PCT publication.

3 One of the differences is that the PCT publication, as Example 4 in the
4 PCT publication is not present in the provisional. But that as I mentioned,
5 the PCT publication is still, it's prior art to the 306 Patent.

6 JUDGE VALEK: Are there any other substantive differences
7 between the two documents?

8 MR. HOLMAN: The Example 4 is one addition to PCT. There's
9 another example in the PCT which is referred to as Example 2, which is not
10 the same Example 2 that's in the provisional. The PCT inserted an
11 additional example in between the provisional Examples 1 and 2. So there's
12 two, Example 2 and Example 4 in the PCT are new compared to the
13 provisional. Aside from that there's no substantive differences. And even
14 then, the examples just convey or further confirm the disclosures that were
15 already present in the provisional. It's not, I'd say it's more cumulative
16 disclosure rather than new.

17 JUDGE VALEK: It has a couple of additional examples?

18 MR. HOLMAN: That's correct. If I could direct the Board's
19 attention to Slide 28, please. Here I just wanted to point out that the
20 Petition's arguments, the Petition, and this is the box on the left on Pages 31
21 and 32 of the Petition. The Petition argued that Schmitt discloses mapping
22 the consensus reads and mapping the raw sequence reads. You can see this
23 in the highlighted text, on the first portion of the highlighted text, the
24 Petition says, "Schmitt discloses that reads were aligned to the human
25 genome with the Burrows-Wheeler Aligner."

1 And on the right, the box on the right, that's the disclosure from
2 Schmitt, so it's Paragraph 60. And you see the quoted text there at the
3 beginning and Schmitt says, "The consensus sequences were then paired
4 with their strand-mate." So that is a mapping of the consensus sequence
5 reads, we're not disputing that.

6 But the next sentence, if you go back to the Petition's argument, the
7 next sentence says, "Schmitt also discloses mapping the raw sequence
8 reads." And Petition refers to a different portion of Schmitt, now it's
9 referring to this disclosure in Paragraph 66, where Schmitt says the
10 mutations were initially scored without considering SMI sequences.

11 So the point here is that the Petition did acknowledge the difference
12 between mapping consensus sequence reads and mapping raw sequence
13 reads and explained that Schmitt teaches both. And as I mentioned earlier,
14 both of these were enclosed in Schmitt, claiming those mapping steps. At
15 least because the 306 Patent makes it clear that the mapping can occur
16 before or after the collapsing step. This is shown on Petitioner's Slide 32.

17 So as you can see here, again, the claim language is on the left, and it
18 has this comprising step, which I mentioned means somewhere in reducing
19 or tracking redundancy there's this mapping step. And the disclosure on the
20 right is from the 306 Patent where the patent says, "collapsing, reducing, or
21 tracking redundancy can be performed before or after mapping, and in some
22 aspects collapsing can be performed before mapping." And this is also
23 evident in the patent's Figure 1, which is this workflow overview. And it
24 says in Step 108 there that's highlighted, "Refers to reducing, reduce or
25 track redundancy of reads," which is generally consensus sequence reads.
26 And then the following, Step 110, says "map reads to selected locus or loci

1 in the genome.” What reads is it mapping here, it’s mapping the consensus
2 sequence reads that were just generated and reducing or tracking
3 redundancies step.

4 So in other words when Claim 1 says mapping a subset of the
5 plurality of sequence reads to the referenced sequence, they include mapping
6 the raw sequence reads and mapping consensus sequence reads, as opposed
7 to the reference sequence.

8 Okay. The other aspect of Claim 1 we haven’t got to yet is
9 determining the distinct cell-free molecules based on paired reads over the
10 unpaired reads. So let’s take a look at that claim language. That’s in Slide
11 35. So the key word in this claim element is “or,” the one we have the red
12 box around. The Board noted this in its decision on this Petition. And that
13 in the determining of these distinct cfDNA molecules is based on paired
14 reads or unpaired reads.

15 And beginning with the paired reads, if you can turn to Slide 36, the
16 Petition explained or established that Schmitt discloses determining distinct
17 molecules based on paired reads. For example you see here as reflected in
18 Schmitt’s Figure 3, depicts determining these distinct molecules based on
19 paired reads. And you can see that it’s in the reads that are grouped into
20 Column A, B, and C. And as Dr. Spellman explains in the text box to the
21 right, this is from his declaration, this figure depicts the sequence reading
22 grouped into paired families, and that each family pair reflects one double-
23 stranded DNA fragment. So this is determining distinct molecules, distinct
24 DNA molecules based on paired reads. And as I mentioned, the Board
25 correctly noted in its decision on institution, which we have excerpts of in
26 Slide 37, that this disclosure in Schmitt referring to the paired reads, that’s

1 enough to beat this claim limitation because of the word “or” in its claim
2 language.

3 So the Board doesn’t even need to reach the question of whether
4 Schmitt determines distinct DNA molecules based on paired reads, excuse
5 me, based on unpaired reads, for its analysis of Claim 1.

6 All right. Moving on I’d like to address first a POSA’s reason to
7 combine Schmitt and Narayan. So let’s turn to Slide 60, please. So the
8 Petition showed that if the POSA would have been motivated to apply
9 Schmitt’s error correction methods when sequencing cell-free DNA such as
10 that taught in Narayan. And Narayan is Exhibit 1082.

11 Narayan disclosed a method of analyzing cell-free DNA from human
12 blood samples. But despite using the word “ultra sensitive” in the title of the
13 article, Narayan recognizes its methods had room for improvement, right.
14 Narayan reported that it had a limit, its methods had a limit of detection of
15 approximately one in 5,000 molecules. And Narayan acknowledged that
16 much work remains to be done in hope that someday producing a product or
17 an assay that could be used to guide clinical decisions.

18 So as the Petition explained, a POSA would have been motivated to
19 apply Schmitt’s error correction methods to bridge this gap. A POSA would
20 have understood that using Schmitt’s duplex sequencing methods would
21 improve the sensitivity of sequence detection and thus the POSA would have
22 been motivated to use Schmitt’s methods in Narayan’s clinical applications.

23 Now Patent Owner raises two primary arguments about this reason to
24 combine Schmitt and Narayan. One relates to the efficiency or sensitivity of
25 Schmitt’s methods, and the second relates to the environment or the settings.

1 If you could turn to Slide 62, please. Here we have an example of
2 Patent Owner's argument referring to Schmitt's method where Patent Owner
3 says it's not particularly sensitive, it's unreliable for detecting cancer
4 mutations in a clinical setting. Now I'm going to address each of these
5 arguments in turn with my remaining time I have here.

6 First I'll address the sensitivity or the unreliability of Schmitt's
7 methods, Schmitt's assay. If you could turn to Slide 63, please. So one of
8 Patent Owner's arguments is that Schmitt's method is not sensitive enough
9 because "zero mutations were identified in Schmitt's Example 1." But as
10 Petitioner explained in its Reply, Schmitt's Example 1 started with normal
11 human DNA, normal human colonic mucosa. That's in Schmitt in
12 Paragraph 52 which you can see to the right.

13 And Patent Owner's expert, Dr. Hagemann, testified, this is from this
14 Declaration, that DNA samples such as this normal colonic tissue is
15 expected to contain no somatic mutations. So Schmitt's results here where
16 they detected zero mutations, really ultimately means, and a POSA would
17 understand this, that Schmitt detected zero false positive mutations, which is
18 actually a good result when you're sequencing normal human DNA. And
19 moreover, the box in the bottom right, Schmitt also identifies ways of
20 improving its assay even further.

21 Additionally, a POSA would have known from the general knowledge
22 in the art that Schmitt's methods worked. This you can see for example in
23 Slide 64. The authors of the Schmitt patent application have an article we
24 refer to as Schmitt 2012. This is Exhibit 1064. Which shows that Schmitt's
25 method, or discloses that Schmitt's method, duplex sequencing methods,
26 represented 10 million-fold in improvement over standard methods in the

1 art. So a POSA would have been aware of references like Schmitt 2012,
2 also the Kivioja reference, which is Exhibit 1008, which refers to Schmitt's
3 method as potentially an axiom to accuracy sequencing cell-free DNA. A
4 POSA would have known, would have been aware of this general
5 knowledge, these disclosures in the art and would have expected and
6 understood that Schmitt's methods do work as intended.

7 The other prong of Patent Owner's arguments against reason to
8 combine Schmitt and Narayan relate to the so-called clinical settings.

9 JUDGE VALEK: Counsel, before you move on to that I have a
10 question. Because Dr. Quackenbush, if that's how you pronounce his name,
11 calculates in Schmitt's Example 1 that it produces duplex consensus
12 sequences for only about two molecules out of every billion DNA fragments
13 tested. And that means that the data for trillions of DNA molecules are lost.
14 That's in his expert declaration, Exhibit 2015. Does the Petitioner dispute
15 that calculation, and if so, is there evidence in the record that shows that
16 those calculations are incorrect?

17 MR. HOLMAN: Well, Petitioner doesn't dispute that Schmitt's
18 methods do result in an overall reduction of sequence molecules, right, that's
19 part of Schmitt's workflow and its process.

20 JUDGE VALEK: And let me, before you move on, do you dispute
21 his calculation of the magnitude of that reduction in molecules? That's what
22 I'm asking when I say he calculated it and it's not just a little reduction, at
23 least it sounds like quite a bit. And so I'm asking if you have any evidence
24 that says his calculation of the magnitude of the loss of molecules, at least in
25 Schmitt's Example 1, is incorrect?

1 MR. HOLMAN: No, Your Honor, Petitioner did not dispute Dr.
2 Quackenbush's calculations, but Petitioner does of course dispute Dr.
3 Quackenbush's implications that these calculations are a detrimental impact
4 to a POSA's view of methods. And that's where Petitioner's claim that a
5 POSA would have understood you're going to end up with less sequence
6 molecules based on Schmitt's workflow and Schmitt's methods, but the
7 molecules you end up with are extremely valuable due to the accuracy of
8 Schmitt's methods, which are orders of magnitude better than the previous
9 correction methods.

10 JUDGE VALEK: Is there a distinction between the word "accuracy"
11 and "sensitivity"?

12 MR. HOLMAN: Probably there would be a subtle distinction.
13 Schmitt refers to error correction and accuracy, Schmitt also refers to
14 sensitivity. So I think sensitivity is more being able to detect a rare instance,
15 you know, whether one molecule out of many, many, many molecules, right.
16 So that's being very sensitive to detect that rare mutation. Whereas accuracy
17 is being able to accurately detect the mutations based on like a sequency
18 accuracy. So you're reducing errors. For example distinguishing which was
19 the error in a mutation, that's more accuracy versus detecting the rare
20 molecule. So it's like there's overlap between the two but there are some
21 differences.

22 JUDGE VALEK: So error correction would go more towards
23 accuracy?

24 MR. HOLMAN: Yes, Your Honor.

25 JUDGE VALEK: Okay. Now I understand your argument that
26 Schmitt's method is designed to filter out data, sort of by design, in order to

1 increase accuracy through error checking. But isn't there a point where one
2 filters out too much data such that Schmitt's DCS method might not be the
3 best choice of sequencing methods in a scenario where you have a more
4 limited supply of input DNA, such as might be the case with cfDNA?

5 MR. HOLMAN: Well I think we would disagree with that position,
6 Your Honor, that as the Petition explained, even if you're starting with a
7 limited amount, Schmitt provides methods of increasing the amount of input
8 DNA so in the event there's limited input you can, you know, perform
9 methods such as targeted enrichment or additional amounts of PCR which
10 helps boost up the input DNA that you're going to put through Schmitt's
11 processes. And so while there is a reduction of sequence molecules in
12 Schmitt's workflow, a person of ordinary skill in the arts is not going to see
13 that as this deterrent from implementing Schmitt's error correction methods
14 when they're using cell-free DNA.

15 So just briefly with the last minute or so of time I'd like to address the
16 issue of clinical settings. And as I mentioned, Patent Owner argues that
17 Schmitt's methods wouldn't be suitable or applicable in a so-called clinical
18 setting. As Petitioner's explained in their Reply, Patent Owner has really
19 mischaracterized the Petitioner's arguments as being narrowly limited to
20 only apply Schmitt's methods in a strictly regulated setting, which
21 essentially amounts to requirement like approved diagnostic care.

22 And all this is in an attempt to drive a wedge between Schmitt's
23 methods and Narayan's sequencing of cell-free DNA. But if you look at the
24 Petition, for example Page 35, the Petition explained that a POSA would
25 have been motivated to apply Schmitt's error correction methods combined
26 with Narayan to improve the sensitivity in clinical settings as suggested by

1 Narayan. So Petition's referring to Narayan's settings here. In Narayan was
2 in a clinical setting so to speak, to the extent that it involved human patients
3 who went to a clinic or a doctor's office or a hospital to have blood drawn,
4 which was then sequenced. But Narayan's tenants and Narayan's
5 application and its methods was not using, you know, approved diagnostic
6 kit to diagnose patients or guide clinical decisions in Narayan.

7 So for these reasons, that's the proper context of the Petition, was
8 asserting this combination. And then as we mentioned in the Reply, Patent
9 Owner uses the phrase "clinical settings," to import this higher standard
10 there that while it's included in the Petition, POSA would have concluded
11 that in their motivation, it's certainly not the limit of Petition's readiness.

12 So I'm a little bit over time here so if any of the judges have any
13 questions I'm happy to address them. Otherwise, I'll save my remaining
14 time for rebuttal.

15 JUDGE MITCHELL: I do have one quick question. So if we agree
16 with Patent Owner that Schmitt really doesn't have improved sensitivity, do
17 you have any other motivation to combine the teachings, or is that it as to
18 motivation, is to improve the sensitivity is therefore somehow applied to
19 Narayan?

20 MR. HOLMAN: Well it is a motivation that is included in the
21 Petition to improve sensitivity, but I think the Petition has other rationales
22 that would, whether it's enhancing the accuracy such as what's disclosed,
23 you know, what's understood in the art from the Rahita (phonetic) reference.
24 And just to be clear, Schmitt itself discloses a sensitivity that's greater than
25 Narayan's. So if you look in Schmitt's, for example, it's Example 2, which
26 is a sheared end example, but it has a mutation, it discloses detecting a

1 mutation frequency of about 5.33 times 10 to the minus fit. That's about a
2 one in 19,000 molecules compared to Narayan's sensitivity of 1 in 5,000
3 molecules. So Schmitt itself discloses a sensitivity that's better than
4 Narayan, and that's straightforward for a POSA proving Narayan's methods.

5 JUDGE MITCHELL: Thank you.

6 MR. HOLMAN: Thank you.

7 JUDGE MITCHELL: And we'll certainly give you your full 20
8 minutes to add on to your rebuttal time.

9 MR. ROSATO: Ready?

10 JUDGE MITCHELL: Yes, whenever you're ready.

11 MR. ROSATO: Okay. Thank you. And may it please the Board, and
12 thank you for having us here again. Can you turn to Slide 5, please. I'll
13 start here.

14 Just for contextual purposes, I just want to say a word about the
15 reminder about the prosecution's history here because it does provide some
16 context. And this is recognized in the Institution Decision. But the Schmitt
17 disclosure was before the examiner and dealt with during prosecution, in fact
18 it was cited in several office actions. And as noted, the claims were
19 specifically amended to differentiate from the disclosure of Schmitt, and
20 ultimately were. And I mention this again for contextual reasons, not to
21 suggest that we're not somehow allowed to revisit the reference, certainly
22 we are. But these are claims that were drafted with Schmitt right in front of
23 the applicant in the office. And the verbiage, the language of the claims,
24 was written to draw distinction between the subject matter Schmitt. And as
25 we move through the language of the claims, we see that that remains true.

1 Turn to Slide 6, please. A summary slide here, but some of these
2 aspects that do distinguish from Schmitt in our representative claims we'll
3 cover in more detail, but include the claim recitations regarding the tagging
4 with the duplex tag with exogenically attached to the DNA molecule and
5 with the molecular barcodes being in that attached duplex tag. The
6 distinctions are represented with the numerical requirements regarding
7 molecular barcodes, that's the limitation with the number, and drawn to the
8 molecular barcodes.

9 The mapping limitation of the claims, and then when we get to Claim
10 17 the sorting of the sequence reads into paired sequence reads and unpaired
11 sequence reads. We'll also talk about motivation. But I do want to address
12 the limitations issue. I think this is ultimately, you know, there are multiple
13 dispositive issues but this should really be one of the primary dispositive
14 issues and one that really has no rebuttal. I heard some new argument here
15 today, I want to go through that.

16 Let's turn to Slide 7, please. But as the briefing stood there was no
17 real rebuttal to this argument that should really draw a distinction between
18 the subject matter of Schmitt. This starts with the claim element regarding
19 the tagging. Let's move on to Slide 8, please.

20 So just to summarize the issue, and I think, you know, this has been
21 recognized based on the discussion we heard earlier. But to summarize the
22 issue, the Petition relies specifically on Schmitt's hybrid embodiment.
23 There's Schmitt's primary embodiment and then there's this hypothetical
24 hybrid embodiment that's in Schmitt, and that's the embodiment that the
25 Petition challenge relies on. So it's important to keep the different
26 embodiments straight as I think in some aspects of the argument, the

1 briefing, there's, you know, conflation between those two. But the Petition
2 challenge, to be clear, is relying on this hybrid embodiment. And in that
3 hybrid embodiment we know what the molecular barcode is, and we heard,
4 you know, more of that today. The molecular barcode is the combination of
5 this exogenous tag sequence plus the endogenous DNA sequences. Those
6 sequences, those components together form the molecular barcode, and the
7 hybrid embodiment. And the claims --

8 JUDGE VALEK: Let me just interrupt you for a moment.

9 MR. ROSATO: Sure.

10 JUDGE VALEK: So the Petition, I think very clearly identifies in the
11 3-mer, so just the 3-mer portion of the hybrid SMI as the molecular barcode
12 in Claim 1. That's what it says. And so maybe it would make more sense
13 for you to address that contention.

14 MR. ROSATO: Yeah, and that's all part of this, and this all starts
15 with the language of the claims. And maybe I'm covering things that I'm
16 speaking the obvious here, but just to start with the language of the claims. I
17 agree, Your Honor, that's where we have to go with this. But the language
18 of the claims, which we'll come back to and compare with the hybrid, the
19 language of the claims distinguishes between the DNA molecule and the
20 duplex tag, it specifies that the duplex tag is attached, and it specifies that
21 the molecular barcode is the duplex tag.

22 As we look at the cited hybrid of Schmitt, I agree they mapped the n-
23 mer portion, but the n-mer portion is not the molecular barcode. And if they
24 want to come back, there's a lot that happened between the Petition and then
25 through discovery and the trial phase and where we are now, they seem to
26 want to ignore all of that. We should talk about it, they want to ignore all

1 that and just go back to some comment in the specification that refers to it as
2 an molecular barcode. But a lot has happened since then.

3 And it's not just, even if we start with Petition materials, it's not just
4 the portions they point to that's called molecular barcode. There are also
5 other portions that are pointing to the combination and calling that the
6 molecular barcode. An example of that is in Dr. Spellman's Declaration
7 where, you know, he, throughout the Declaration he's referring to the alpha
8 and beta SMI sequences of the molecular barcode. And he does that in
9 examples in Paragraph 300 for the bottom. He states, "Schmitt teaches that
10 each family is grouped by the order of their molecular barcode tag sequence,
11 alpha beta or beta alpha." And in that he's citing to Paragraph 30 of the
12 Schmitt provisional, which is the hybrid embodiment they're referring to.

13 So, yeah, we start with the Petition materials. We know what they're
14 mapping, but as we went through the discovery process we see that
15 sometimes Dr. Spellman is saying different things, which is precisely why
16 we conduct discovery on these issues, which we did. And we asked Dr.
17 Spellman what is the molecular barcode. And he answered that that's the
18 alpha and beta SMI sequences.

19 We went through this same exercise in a co-pending case with Dr.
20 Satija. We submitted that deposition transcript and Dr. Satija testified that
21 it's the SMI sequences that are the molecular barcodes in Schmitt. And in
22 that case there's a reason why they never disputed this, because in that case
23 they were adamantly arguing that there's a difference between a molecular
24 barcode and just any barcode. And they even repeated some of that here.

25 So as of the Petition material stage of this case, they kind of were all
26 over the place on this issue. We conducted discovery and we settled on what

1 their experts, with our experts, what exactly is the molecular barcode in
2 Schmitt's hybrid. And it's the combination of the components, it's the
3 combination of endogenous sequence and that endogenous tag sequence. So
4 that's not in dispute. We laid this all out in the Patent Owner Response, it's
5 in, you know, there was no claim construction of molecular barcodes in the
6 Petition. We addressed this during discovery, we addressed this in our
7 Patent Owner Response briefing, it's even addressed in the claim
8 construction section under the section Molecular Barcodes.

9 In there we pointed out that all the experts are agreeing precisely what
10 is the molecular barcode in Schmitt's hybrid embodiment, and it's the
11 combination. It's not this, you know, this single piece. We don't get to pull
12 out, you know, one piece of a barcode sequence and then sort of anoint that
13 like the barcode.

14 So that's where the Patent Owner Response, we encourage the Board
15 to go back and look at the Petitioner's Reply on this issue. Because there's
16 absolutely no dispute from Petitioner as to the molecular barcode issue, what
17 constitutes molecular barcode in Schmitt.

18 JUDGE VALEK: Let me ask you a follow-up on that. Suppose that
19 we were to look at the argument that Petitioner made in its opening today
20 where they identify just the 3-mer as the barcode, which seems to be also
21 what they're saying, at least on Page 28 of the Petition. Is there a reason, if
22 we assume that the 3-mer is what they're mapping to the molecular barcode,
23 is there a reason why that mapping doesn't meet the language in Claim
24 Element 1B?

25 MR. ROSATO: Well it's not a molecular barcode.

26 JUDGE VALEK: And why isn't it a molecular barcode?

1 MR. ROSATO: It's not a barcode that distinguishes one molecule
2 from the other. So that's --

3 JUDGE VALEK: So is there a definition in the patent or something
4 in the specification of the 306 Patent that says that the molecular barcode has
5 to uniquely identify each molecule, each fragment?

6 MR. ROSATO: Okay. So, right, so I want to be clear here, I don't
7 want to be in the position of being asked to, you know, give definitions for
8 the first time in oral argument. So, you know, and I don't say that to push
9 back on your question, I'm happy to answer it. But just understanding the
10 context here. This is a Petition that had no construction of this term. We
11 explored, you know, what constitutes the molecular barcode with the
12 experts, and this is what we settled on, and pointed that out in our briefing.
13 In their Reply they don't dispute that at all. They do have a different
14 argument and I want to get to that, but they don't dispute what constitutes
15 the molecular barcode of Schmitt.

16 So I would say that's a situation where there's an obvious agreement
17 between parties as to what precisely in the art is the molecular barcode. And
18 we don't have any pushback on that, so if they wanted to make this work
19 with a definition, that's something they should expand. So that being said, I
20 mean your question was is there an express definition of the term "molecular
21 barcode" in the 306 Patent. I'm not aware of one but, you know, we haven't
22 been forced, but by the way the records developed, the parties haven't been
23 forced by Petitioner's case to, you know, tee up a construction petition and
24 go through the normal process, even that type of process on this. So I'm a
25 little hesitant to try to, you know --

1 JUDGE VALEK: This is where I'm struggling, counsel. I'm
2 struggling because I'm looking at the Petition and it very clearly says the 3-
3 mer, in a 3-mer hybrid tag method the 3-mer is the molecular barcode, and
4 then it does a calculation for the wherein clause for the N number based
5 upon that. It says therefore we meet that because with 3-mer barcode itself
6 meets that limitation. And so that's their contention in the Petition. You're
7 telling me that that does not meet the claim language because that 3-mer all
8 by itself is not a molecular barcode. And so I need to know what is your
9 basis for that argument?

10 MR. ROSATO: Several bases, Your Honor. As we go through the
11 Petition materials you pointed to something where they identified 3-mer as
12 the molecular barcode. There are other areas in the Petition materials where
13 they identify the SMI as the molecular barcode. So they state both, right, so
14 that's an inconsistency, and that was one that was explored during discovery,
15 and we got clarification on that that it is not the n-mer sub portion that's the
16 molecular barcode, it's the combination of the molecular barcode. And at
17 that point, you know, we understand where the defect is in their Petition.
18 They point, some places they pointed to the wrong thing, some places they
19 pointed to the right thing. And now we know what the right thing is in
20 Schmitt, it's the combination, that's the molecular barcode. And if we're
21 going to map or try to trace the molecular barcode that's what we should be
22 pointing to. Otherwise, you know, it sort of renders the term meaningless.
23 We get to a point where we can pull out, you know, any nucleotide sequence
24 from anything and call it a molecular barcode, and clearly that's not correct.
25 So we know what the molecular barcode is after that. And I'd say that
26 should be sufficient.

1 JUDGE VALEK: What's the molecular barcode in your patent
2 though?

3 MR. ROSATO: In the claims it's the sequence that's in the duplex
4 tag and is used to distinguish one molecule from another.

5 JUDGE VALEK: It's uniquely distinguished?

6 MR. ROSATO: It's not a sub portion of, you know, of something
7 that's actually used to distinguish.

8 JUDGE VALEK: Okay. And so the barcode itself needs to be what
9 uniquely distinguishes the fragment, according to your view of the
10 specification and your patent?

11 MR. ROSATO: I mean again I'm hesitant as a non-moving party to
12 try to offer some construction when they didn't offer a construction and we
13 have agreement between all the experts as to what constitutes the molecular
14 barcode. And nobody's suggesting that you could just arbitrarily identify it
15 and throw up your hands and call it a molecular barcode. And that's sort of
16 what they're asking you to do. So.

17 JUDGE VALEK: Yeah, but the specification of the patent, as
18 Petitioner pointed out in its opening, refers to barcodes, it uses that word.
19 And it says that in one embodiment you could use the combination of the
20 barcode and some of the endogenous DNA to identify the fragments.

21 MR. ROSATO: Yeah. And I want to be careful about that because,
22 and this is why, you know, this is precisely why it's important to follow this,
23 you know, this process in the case where the Petitioner bears the burden on
24 these issues. But I want to be careful with that because the specification
25 does also discuss index or sample barcodes and as you heard here today, and

1 as we heard ad nauseum in the co-pending case, that there's a big difference
2 between an index barcode, and a molecular barcode.

3 And, you know, there is a difference between them so when they're
4 referring to something in the specification that uses the more generic term
5 "barcode," I'd want to be really careful with how that's used.

6 JUDGE VALEK: Okay. So I'm asking you for Patent Owner's
7 position, and let me make it a little bit more specific. This is in Column 21
8 of your patent, Exhibit 1001, it refers to an alternate method, says
9 alternatively, a polynucleotide can be uniquely identified by the combination
10 of a "DNA barcode and one or more endogenous sequences of the
11 polynucleotide." And so it uses the word "barcode" there, calls it a DNA
12 barcode. Is that reference to a DNA barcode in Column 21 something
13 different than the molecular barcode in the claims?

14 MR. ROSATO: Well, I mean by the terminology of the claims, it is.
15 The claim term is molecular barcode. And again, what they're pointing to
16 here is a term barcode, right? So the DNA is a molecule.

17 JUDGE VALEK: I'm struggling to understand the distinction, and I
18 just want to know what your position is, counsel.

19 MR. ROSATO: Our position is the hybrid method on which they rely
20 does have a molecular barcode and that molecular barcode is exactly what
21 all the experts said it is, which is the alpha and beta SMI sequence, not the n-
22 mer sub portion. If they're pointing to the end or sub portion, they're
23 pointing to the wrong thing. So that's our position.

24 JUDGE VALEK: So the contention in the Petition, I understand that
25 you think they've shifted, but if we were to interpret that as an alternate

1 theory they are arguing that the 3-mer is the barcode in your claim. Do you
2 have an argument or a contention that that's wrong --

3 MR. ROSATO: Yeah.

4 JUDGE VALEK: -- and if so, what is that argument?

5 MR. ROSATO: Sure. Understood. I actually do think they're
6 pointing to the 3 nucleotide end mer of a hybrid embodiment and calling it a
7 molecular barcode in some places. And I think that's inconsistent with what
8 they say in other places. I think ultimately that contention is incorrect. And
9 in other places they refer to, they correctly refer to the SMI of Schmitt as the
10 molecular barcode. And that's true as we look at everything they state about
11 Schmitt, everything Schmitt says about Schmitt, they're using their SMI
12 sequences to sequence reads and distinguish molecules. It is the SMI that's
13 the molecular barcode. So, you know, in places where they have pointed to
14 the n-mer sub portion and called that a molecular barcode, that's incorrect.
15 In the places where they pointed to the SMI sequence of Schmitt and called
16 that a molecular barcode, that is correct.

17 So that's our position. So, yes, we agree they're relying on the n-mer
18 sub portion in some places but that's inconsistent throughout their materials
19 and it's ultimately not consistent with the preponderance of the evidence in
20 this case, which all points to this combination SMI being the molecular
21 barcode. So to the extent they're pointing to the sub portion, they're
22 mapping the wrong thing. So that's our position. I hope that's clear.

23 JUDGE VALEK: Thank you.

24 JUDGE HULSE: Counsel, you refer to the "co-pending case" several
25 times, I just wanted to make clear that you're referring to the 1158 IPR or is

1 there some other case that you're referring to it? There are like 14 cases
2 between yourselves.

3 MR. ROSATO: Fair point, Your Honor. Let me make sure I've got
4 the one. We submitted the transcript from Dr. Satija in this, and my co-
5 counsel tells me it's 817.

6 JUDGE HULSE: Thank you.

7 MR. ROSATO: Yeah. IPR2022-00817. Thank you.

8 JUDGE MITCHELL: Can I ask you, I'm kind of visual, and it looks
9 like you have the Schmitt figure on your Slide 14. Can you show me what
10 you're saying is the molecular barcode?

11 MR. ROSATO: Yeah. Great. Thank you, Your Honor. Turn to
12 Slide 14. Right. So this is consistent with exactly what my friend for the
13 Petitioner stated today. The duplex, so on the right side of exhibit, this is
14 Slide Number 14, Your Honors. And on the right side of this is the image or
15 the illustration that's found at Page 9 of the Petition. And this is Petitioner's
16 illustration of what Schmitt's hybrid embodiment looks like. This is not
17 Schmitt, this is their illustration.

18 So what they're identifying as the duplex tag here starts at the yellow,
19 right, it's the Y shaped adaptor and ends at the yellow. It ends where it
20 meets the DNA molecule. So they're not saying, as we heard them say here
21 today, the duplex tag is not the DNA molecule, it's what's attached.

22 In this hybrid embodiment the molecular barcode, or the SMI, is
23 marked by the circle region here, which picks up part of the duplex tag and
24 part of the DNA molecule.

25 JUDGE MITCHELL: And you agree with that, it being the molecular
26 barcode?

1 MR. ROSATO: I agree, yes, that that circled combination is the
2 molecular barcode in Schmitt's hybrid method. And that is the method they
3 rely on.

4 JUDGE MITCHELL: Thank you.

5 MR. ROSATO: And while we're on this slide, just to put a bow on
6 this point, the reason why we're saying this doesn't map to this claim, this
7 embodiment is excluded from this claim, is based on the language that
8 distinguishes between the DNA molecule and the duplex tag, and specifies
9 that the duplex tag is attached, and it's that duplex tag that comprises the
10 molecular barcode. So we don't see that here, right? Here in the hybrid
11 embodiment, unlikely the barcode is not within the duplex tag, it's this
12 hybrid portion of the DNA molecule and a portion of the tag, it's together.
13 That should be excluded from this claim based on the language of this claim.

14 JUDGE MITCHELL: Thank you.

15 JUDGE VALEK: Counsel --

16 JUDGE VALEK: Go ahead, Judge Mitchell.

17 JUDGE MITCHELL: No, I just was saying thank you. Go ahead.
18 Sorry.

19 JUDGE VALEK: I was going to say, so it's your position that the 3-
20 mer is attached to the fragment, but the molecular barcode, which is the
21 combination of the 3-mer and the end, is not attached to the fragment
22 because it's actually part, or not attached to the fragment because it actually
23 contains part of the fragment?

24 MR. ROSATO: I think I would say it a little differently. The claim
25 requires, specifies the duplex tag, I'll use the term exogenously attached,
26 meaning it's not the DNA molecule, it's something else that gets attached.

1 And the claim specifies that the molecular barcode is in the duplex tag. Our
2 position --

3 JUDGE VALEK: It doesn't say, counsel, it doesn't say exogenously
4 attached, and that's why I'm struggling with when you say that the claim
5 says that, it doesn't. It says attached.

6 MR. ROSATO: I know. That's why, thank you, Your Honor. I
7 caught myself when I said I'm going to say exogenously attached. I'll stick
8 with the claim language. The claim says there's a DNA molecule and
9 there's a duplex tag, and a duplex tag during the tagging process gets
10 attached to the DNA molecule. It's different than, rather than use the word
11 exogenously, I'll say that the DNA molecule and the duplex tag are two
12 different things. Right. And the claim requires the molecular barcode to be
13 in the duplex tag, which is separate from the DNA molecule.

14 And this is all deliberate, right? Again, this is why I started by saying
15 when this claim was drafted Schmitt was right there, so this wasn't lost
16 during the drafting process. The claims were amended and drafted to
17 exclude Schmitt, and there's a reason why this type of language was
18 selected. You know, the applicant's deliberately trying to exclude a piece of
19 prior art that the examiner is asking you to distinguish from, and I think they
20 did this.

21 JUDGE VALEK: But in Schmitt though, as I understand it, the X
22 portion, the 3-mer, is attached to the fragment, correct?

23 MR. ROSATO: The X portion.

24 JUDGE VALEK: I'm looking at your Slide 14, which is from the
25 Petition that we discussed earlier.

1 MR. ROSATO: Yes. Yes, they've invented new terminology here
2 but, yes. What they're pointing to there at the X, that's not the molecular
3 barcode, but it is a portion of the tag. I'll call it the detection adaptor, it's
4 part of that washing adaptor.

5 JUDGE VALEK: And so in your view the entirety of the tag needs to
6 be attached in claim Step 1B? Go ahead, I'm sorry.

7 MR. ROSATO: So in my view the claim in Element 1A references a
8 DNA molecule. And then in Element B it refers to tagging and the tagging
9 process is attaching a duplex tag. So I think the claim makes clear that the
10 DNA molecule and the duplex tag are two different things. One gets
11 attached to the other, right. Yeah, sorry.

12 JUDGE VALEK: And so the tag has to be entirely separate from the
13 molecule because they're two separate things. What I'm struggling with is,
14 it seems like in your view, what you're saying the Petitioner is saying as
15 well, is the tag is the combination of the 3-mer, which is exogenous, and a
16 portion of the endogenous DNA in the fragment. And so everyone seems to
17 agree that in Schmitt's process the 3-mer does get attached and in that sense
18 it is being tagged. But what you're saying is the claim distinguishes that
19 because the duplex tag, all of it needs to be exogenous, none of it can be part
20 of the DNA fragment itself.

21 MR. ROSATO: I think that's correct by the language of the claim.
22 You've got two separate objects, one gets attached to the other, that means
23 they can't be the same object. But, you know, to be clear, I agree with your
24 question, Your Honor, that there is a potential ambiguity in the sentence you
25 read. Our understanding as we moved through it was consistent with
26 counsel's answer today, when they answered that, you know, what they label

1 here as the L and the R portions, are not part of the duplex tag here, they're
2 not part of that Y shaped adaptor, those are part of the molecule. So I think
3 they answered that honestly today. They tried to walk it back a little bit
4 once they saw where you were going with that, but that was correct. You've
5 got the DNA molecule, you've got the tag, those are two different things.
6 And I would agree with their first answer, which was to candidly
7 acknowledge that those are different.

8 Okay. I do like process, and I know the judges do too. It's very
9 important in these, especially when you're, you know, everybody can
10 sympathize with the patent owner because there's good reason this room
11 plays. But for that reason I do want to submit, maybe I'm beating a dead
12 horse here, but I want to make sure that there is recognition here how this
13 issue had developed and what the response was in the briefing. And with
14 that I'll turn to Slide 15 and then we can move on from this issue.

15 But again, we addressed, we talked to the experts about the molecular
16 barcode issue, and we addressed this in the briefing. And I would very
17 much encourage the Board to look at the Petitioner's Reply Brief. They do
18 not dispute the molecular barcode characterization in that aspect. Their only
19 argument here, their argument in the Reply, is to come back and they assert
20 that there's an express definition for the term "duplex tag." So they're not
21 arguing about molecular barcode, they only come back and argue about
22 duplex tags. And their argument is that there's an express definition in the
23 306 specification.

24 As we pointed out in our briefing, we checked that it's improper to
25 argue that they advance an argument regarding any definition of duplex tags,
26 and certainly not express definition. In their Petition materials, if we're

1 going to consider this on the merits, it's pretty easily dispensed with because
2 what they point to as an express definition is what you see here on the slide
3 from Column 17, Lines 9 through 13. This is the sentence that begins "For
4 example." So this is their argument in Reply. They're not arguing about
5 molecular barcodes, they're arguing about duplex tags. And their argument
6 is there's an express definition by virtue of this sentence that begins "For
7 example." So that is their argument.

8 And that argument is easily dispensed with, you know, intent to define
9 and disclaim is not represented here by a sentence that begins "For
10 example." So we would disagree with that new argument that there is an
11 express definition of the term duplex tag.

12 JUDGE VALEK: Certainly, counsel, this statement that you have
13 quoted here on your slide from the patent suggests that tags that differently
14 label the complementary strands of a double stranded molecule, that's at
15 least an example. It may not be the complete extent of the term "duplex
16 tag," but that is one example within the scope of that term.

17 MR. ROSATO: It seems to be some partial functional discussion, like
18 excerpted from the specification. I mean I don't know, they're arguing it as
19 an express definition. There is law that addresses what constitutes an
20 express definition in a specification, and this does not meet this requirement.

21 JUDGE VALEK: But even if we say it's not a lexicographer type
22 definition, that doesn't mean we just get to ignore the intrinsic record. And
23 they did, to their credit, cite this passage in the original Petition. And so we
24 have to do something with it. I'm trying to figure out what is your view of
25 what this language in the specification means because it seems to suggest

1 that a duplex tag can just be something that differently labels the
2 complementary strand.

3 MR. ROSATO: As I indicated earlier, I think it's an excerpt sentence
4 that starts to provide some functional discussion of something, but that
5 doesn't mean it's an express definition. And it certainly does not mean that
6 Petitioner gets to ignore the language of the claims and still argue the
7 specification, which is exactly what they're trying to do. I would again
8 encourage the Board to go look at the Reply Brief and see if you can find
9 some argument that addresses the language of the claim. You won't find it
10 other than the express definition argument.

11 And that's one of the big problems we have with their, both their
12 Petition and their follow-on response is we're going back and pointing a
13 grounding argument in the language of the claims, as we should, and a lot of
14 the responsive argument required when that comes back is repeatedly
15 ignoring that language. This is why we want to draw back to the language
16 of the claims because that's where the analysis really should start.

17 Okay. So a couple other points I want to address. This is an
18 important issue, it's not the only issue. So let's turn to the next slide, 18, turn
19 to 18. So, you know, this is to address a related but slightly different issue.
20 And this goes to the claim's requirement regarding tagging with a number of
21 n different combinations of molecular barcodes.

22 And as we see on the next slide, Slide 19, Petitioner never actually
23 calculates the number of molecular barcodes in Schmitt's hybrid
24 embodiment. At the end of the day they never address this limitation of the
25 claims. Let me turn to Slide 19. So Slide 19 illustrates Petitioner's
26 argument, which can also be found at Page 29 of their Petition, where

1 they're pointing to the, again, the 3-mer portion of a hybrid. And then they
2 argue that 3 nucleotides would generate 4,096 different combinations.

3 Where this comes back to the molecular barcode issue which, as I
4 indicated, really should now be viewed as undisputed that the molecular
5 barcode in Schmitt's hybrid is not the n-mer portion, it's the combination of
6 endogenous and exogenous sequence. So it's for that combination, for that
7 whole molecular barcode, they've never calculated the number of different
8 molecular barcodes. And in fact they don't tell us, and Schmitt never tells
9 us, how many, you know, how much nucleotide sequences in that
10 endogenous portion.

11 And you would need to know that, you would need to know the whole
12 portion if we wanted to calculate the number of molecular barcodes. And
13 we don't have that information. So at the end of the day this is, what they're
14 pointing to is an incomplete hypothetical for this limitation.

15 Let's turn to Slide 20 and address the issue here that Petitioner fails to
16 demonstrate that Schmitt discloses the reducing or tracking redundancy by
17 mapping sequence reads to a reference sequence to defend the challenged
18 claims. And this is fairly straightforward based on the argument in the
19 Petition because there really isn't much argument. Turn to Slide 21.

20 So what's shown here on Slide 21 is the entirety of the argument on
21 this claim element. In the Petition they point to only the Schmitt
22 provisional. By the way the Schmitt PCT was mentioned but it's never
23 mapped to Claim 1. And for this limitation they're relying only on the
24 provisional and only three citations for the provisional, Paragraph 60, 66,
25 and 68. And they argue based on this that Schmitt is disclosing mapping
26 sequence reads to a referenced sequence. And we've gone through each of

1 these paragraphs, our expert has gone through those paragraphs, and as
2 stated in those paragraphs and explained by our expert, and in the briefing,
3 there's a couple problems with those when they're pointing to, what they're
4 pointing to is typically the mention of consensus sequences, right. So as
5 they are in the briefing, they're confusing sequence reads with consensus
6 sequences. So that's particularly true of Paragraph 60 and 68, which are
7 talking about consensus sequences and to the extent they're mapping
8 anything, they're mapping consensus sequences at the end of their process.

9 JUDGE VALEK: Counsel, just for context before you move on. I
10 asked Petitioner the same question, but what does Patent Owner contend is
11 the difference between a consensus sequence and a read, as those terms are
12 used in the 306 Patent?

13 MR. ROSATO: So I appreciate that question, Your Honor. This is an
14 issue, this is the main argument they come back with. And we can move to
15 Slide 24, I should have a slide on this, Your Honor.

16 I was glad to hear them say this today, that there is a difference
17 between a sequence read and a consensus sequence because they actually
18 argue the opposite in their Reply brief, they argue for a special definition of
19 the term "sequence read," such that that term is generically read to include
20 full sequence reads and consensus sequences. So this is important because
21 we have an answer to this from Dr. Spellman, from 306 specification, and
22 from the 306 claims themselves.

23 So Dr. Spellman, in his Declaration supporting the Petition, explained
24 at Paragraph 114, that sequence reads are grouped together, and it's based on
25 those sequence reads that consensus sequence reads are generated. So
26 they're collapsed down to form at each nucleotide, the sequence where at

1 each nucleotide position there is a consensus drawn based on what's
2 recorded in the sequence reads. So those are two different things.

3 We see that illustrated in Figure 4C of the 306 Patent to which Dr.
4 Spellman cites in distinguishing between sequence reads and consensus
5 sequences. And there it shows amplified polynucleotides that are sequenced
6 for sequence reads, those sequences are grouped together and subsequently
7 consensus sequences are generated. That's illustrated in that figure. This is
8 also reflected in the claims, and that's shown here on the slide as well, Claim
9 Element 1D recites sequencing, at least a subset of amplified progeny
10 polynucleotides to produce a set of sequence reads that tell us exactly what
11 the sequence reads are. And then you see in Claim 26, Claim 26 reciting the
12 collapsing of plurality of sequence reads to produce a consensus sequence.

13 So, you know, their main argument in Reply is taking more distinction
14 to interpret the term sequence read to generically encompass both old
15 sequence reads and consensus sequences when that's not correct. Those are
16 different.

17 JUDGE VALEK: What about, I see you're referring to one portion of
18 the specification, but the Reply refers to other portions of the specification to
19 support their argument you just mentioned where they say the terms are used
20 interchangeably. And I believe we saw one in the Petitioner's slides, it's
21 Figure 1. And in Figure 1 they point to Step 108 where it talks about
22 reducing or tracking redundancy of "reads," to correspond to original
23 strands. And then after their Steps 110 and 112, so after you do the
24 collapsing in Step 108 there's Steps 110 and 112. And again, your
25 specification just calls them reads. It doesn't say that these are consensus
26 sequences or consensus sequence reads, it just uses the term reads. And I

1 think Petitioner has pointed to that as an example of how the specification of
2 the challenged patent actually uses the terms kind of interchangeably and
3 doesn't really draw this hard and fast distinction that you seem to be trying
4 to draw for your arguments. So what's your response to that reading of
5 Figure 1?

6 MR. ROSATO: I would say it's a distraction from the process that
7 we're supposed to go through, which is to look at the claim language, and
8 the claim language specifies that it's sequence reads that are back to
9 reference sequence and then the next step of the exercise for Petitioner is to
10 point to the prior art disclosure that shows a mapping sequence reads to a
11 reference sequence as required by the claims.

12 JUDGE VALEK: They did that though, counsel. It seems like this is
13 the same paragraph you pointed to in your slide earlier they pointed to in
14 theirs, it's from the Petition. And the first sentence says, "Schmitt discloses
15 mapping consensus sequence reads," in the first sentence. And then it also
16 discloses mapping raw reads in the second sentence of that same paragraph.
17 And so I'm trying to figure out, and it seems like you've come back in the
18 Reply and said no, no, no, the reads just means raw reads or reads that a
19 consensus hasn't been drawn, there's a distinction between consensus
20 sequence and reads. And they would come back in the Reply and said, no,
21 in fact the specification uses the terms interchangeably. And so it seems like
22 you had a chance to join issue and now I'm just trying to figure out how
23 should we interpret the specification to resolve this particular issue. Because
24 it seems like there's portions of the specifications that support your view and
25 there seems like there's other portions that support the Petitioner's view, and
26 we have to try to figure out what the proper interpretation of those things

1 are. And so since you haven't addressed Figure 1, I want to try to figure out
2 what's your position about that.

3 MR. ROSATO: So I mean, I'm happy to address, maybe I'm
4 confused, but I'm happy to address Figure 1, I was addressing the claim
5 language and the map.

6 JUDGE VALEK: Sure.

7 MR. ROSATO: That's why I was referring to sequence reading and
8 consensus reading because they're two different things in the claims.

9 JUDGE VALEK: In Figure 1 I think you pointed out that it uses the
10 term "reads," right? And specifically I think Petitioner's argument is it uses
11 the term reads in Steps 110 and 112 which seem to occur after Step 108,
12 which is the step of reducing or tracking redundancy, which everyone says is
13 collapsing. And so I'm trying to figure out, you know, how do you reconcile
14 what seems to be disclosed in Figure 1 as just using the term "reads"
15 generally to refer to things even after the consensus has been drawn with
16 your argument that, no, consensus sequence is very different than reads.

17 MR. ROSATO: Okay. Maybe we're talking past each other here on
18 different terminology. You said the term "reads," right? Not sequence reads
19 or consensus sequences or consensus reads, but reads. And it's probably
20 true in the specification they might use the term "reads" generically, that
21 might be true, I'd have to go check. But let's use it for the sake of argument
22 assume that the term "reads" is generically used, that does not mean that the
23 term sequence read is generically used. And that's the term that's in the
24 claim. I'm sorry if I didn't explain that clearly, but that was the point there,
25 that the claims are clear about what's what.

1 If there's a generic use of the term "reads" I'd have to look, you
2 know, I don't know what to say about that other than that's a different term
3 than what's claimed. And honestly it wouldn't surprise me if a read is a
4 more generic term than a sequence read or a consensus sequence, or even a
5 consensus read, if you will. Does that answer your question?

6 JUDGE VALEK: I understand your position.

7 MR. ROSATO: Yeah. And our position further is you don't satisfy
8 the limitations of a claim, Petition satisfies the limitation of a claim by
9 ignoring the language of the claim and pulling out different language from
10 the specification, which seems to be what they're doing, right. And that
11 doesn't work in satisfying the claims, in part of why we put on the slide here
12 to show that the term "sequence read" is clear from Step 1D, the term
13 "consensus sequence" is clearer from Claim 26, and the two things are
14 different. And they point to, in their mapping, consensus sequences. And
15 they may also call consensus sequences reads, doesn't mean they're
16 sequence reads as recited in Claim 1, which they are not.

17 Okay. A couple minutes to address motivation. And this is an
18 important point. And I very much appreciate some of the questions earlier
19 because that saves some time. I did want to spend some time on the two out
20 of a billion to be clear. I'm glad to hear Petitioner agreed with that because
21 part of the way we came up with those numbers is to walk Dr. Spellman
22 through those numbers and those calculations during cross examination. So
23 he confirmed the numbers.

24 And if this wasn't clear, we're looking at Example 1 in Schmitt,
25 which isn't their hybrid method, this is their preferred embodiment where
26 they tell us the amount they start with and the amount that they're able to

1 analyze, and we walked through that calculation with Dr. Spellman. It
2 amounts to analyzing about two molecules out of a billion. So those
3 numbers are accurate, and Dr. Quackenbush agreed with that. And that goes
4 to the sensitivity issue of their preferred embodiment.

5 But one of the things they skipped over in, pardon me, Your Honor,
6 turn to Slide 29. One of the things that Petitioner skipped over in talking
7 about our argument about their motivation was a core step here, and that is
8 while they argue it improved sensitivity in cancer mutation detections and
9 cancer diagnostics, again they were relying on this hybrid embodiment. This
10 is important, this is a critical argument that I think needs to be addressed and
11 not skipped over. And that is, what is the evidence of the sensitivity of their
12 hybrid embodiment? And the answer to that is, there is no evidence. Turn
13 to Slide 31.

14 And this is something we asked Dr. Spellman about during cross
15 examination as well. We went through the Petition materials, and they made
16 a charge of improved sensitivity with this hybrid embodiment as a reason for
17 replacing Narayan. We couldn't find anything, any argument or evidence
18 about sensitivity of the hybrid embodiment because nobody has ever used
19 this, it's not used in Schmitt, there's no information about that either in
20 Schmitt or the Petition materials. And we went through this with Dr.
21 Spellman, and he actually had no answer. He has no idea what the
22 sensitivity is, there's no calculation in the Petition materials. He didn't give
23 any calculation or indication of what the sensitivity is.

24 So ultimately this is an instance of a completely unsubstantiated
25 motivation to combine. The thing that they are arguing as their rationale is

1 not substantiated with evidence. We have no idea what the sensitivity of this
2 hybrid method is, we have no evidence to support that.

3 JUDGE VALEK: Well there is Dr. Spellman's testimony that it's
4 more sensitive. So he may not have quantified it, and I agree with you that
5 he certainly admitted that he didn't do a calculation, but he did testify that
6 one of ordinary skill in the art would understand the Schmitt DCS method,
7 that it would increase sensitivity. I think that's actually what you were
8 referring to in Paragraph 189 of his declaration here and the testimony that
9 you have on Slide 31.

10 MR. ROSATO: Right. So they do argue that, I think we all agree on
11 that, increased sensitivity is their argument and as we explored that issue,
12 there's no evidence of that, certainly not for the hybrid embodiment, right?
13 We need to know what the sensitivity is.

14 JUDGE VALEK: There's no calculation. When you said there's no
15 evidence you're saying there's no calculation, not that Dr. Spellman didn't
16 testify to that.

17 MR. ROSATO: I would say he didn't calculate it. I would also say
18 there is no evidence as to what it is as well, and I can't find any. So fair
19 enough with the distinction, he did mention calculation. And I don't want to
20 conflate those two things. He admitted there was no calculation as, you
21 know, as I report on the evidence here I don't see any evidence of sensitivity
22 for the hybrid embodiment.

23 We did go through the preferred embodiment. Again, they're not
24 relying on, but we're trying to put a finger on, you know, some measure of
25 sensitivity here and that's why we went through this, you know, preferred
26 embodiment to understand this two out of a billion molecule issue because

1 we looked at it, our expert looked at it, and they all, the take on this is it's a
2 terribly insensitive concept. It may have some accuracy for these few
3 molecules that it looks at, but in terms of sensitivity it's extremely poor.

4 And that's really important in the context of medical diagnostics, you
5 know, and we can understand that. If someone goes into a doctor's office to
6 see if they have cancer, you know, there are important ramifications for
7 telling a cancerous patient that they're free and clear. So sensitivity in
8 medical diagnostics is a really important thing, but it's just not substantiated
9 with Schmitt.

10 And then finally, just skip to Slide 37. This is addressed in the
11 briefing. We tried to be thorough in addressing any conceivable rationale
12 that they advance. Some of it was there's some generic comments about
13 how shorter n-mers might be beneficial. So we largely addressed this in the
14 briefing, but its main problem with that, one, most of those comments aren't
15 specific to the hybrid method that they're relying on. They make sort of the
16 generic claim that shorter is better than longer. But tracking that back to
17 support a selection of the hybrid method is where things fall short of a lot of
18 those arguments.

19 The other problem we have with them is, you know, where things do
20 potentially track, or where we're considering the hybrid method, and in
21 trying to do some comparison between their preferred method, there are
22 various sources of evidence that indicate that the hybrid method would be
23 even more error prone and problematic than their preferred embodiment.
24 And we summarize that too. I'll briefly cover it and happy to answer any
25 questions.

1 But two main points on that. One is, yeah there's evidence in Schmitt
2 itself with other references as well that talk about how the n sequences are
3 particularly error prone. All right, so these shear sequences. And Schmitt
4 states that, we say it's the Kennedy reference that states that Petitioner has
5 one of those own references, the Sparclo (phonetic) reference that talks
6 about the next generation sequencing that sequence errors are bias toward
7 the ends of the DNA molecule.

8 So this idea of going from the preferred embodiment that uses these
9 exogenous tags to now incorporating an extra error-prone region of the
10 molecule as the SMI sequence, right. As the sequence that they critically
11 rely on to distinguish their molecules would make it more error prone. So
12 that's one.

13 The other is there is no argument about shorter n-mers being better
14 for, they specifically argued would be better on Illumina instrumentation.
15 Illumina of course is one of the major sequencer, commercial sequencers.
16 We pointed to the Kennedy paper where the same authors have same
17 adventures as that Schmitt had published on their own method, and they
18 report that a tag length of less than 12 is incompatible with the Illumina
19 sequencer because of technical limitations on the platform's phasing
20 requirement and is to be avoided. And that's from the Kennedy reference,
21 those are not my words, those are the words of the inventors who actually
22 had found problems with tags less than 12, usually 10 inches in length.

23 So this all points to, you know, this hybrid embodiment. Again, we
24 try to be thorough in addressing everything that could conceivably looked
25 like an argument for going there, and the evidence all indicates that it'd be
26 more problematic, not less problematic.

1 I'll say, I know I'm keeping in my time but I'll say one other thing.
2 This is just on Claim 17 in this patent. Turn to Slide 40. So at the end of the
3 day so the Institution Decision the Board agreed with us that the Petitioner's
4 material did not establish reasonable likelihood to prevail. I would just
5 note on that, on those claims on those issues that were raised, there has been
6 no material change in the record so that same outcome should be warranted
7 here.

8 But I will point out one thing that was actually fairly important on this
9 point, Slide 43, which isn't addressed, or certainly not rebutted, not even
10 addressed in the Reply materials. Was this issue of sequencing errors in the
11 SMI region. So this argument that was advanced and evidence to support
12 that, including testimony of Dr. Spellman himself, indicating that when you
13 get sequence errors in Schmitt, when there are sequence errors in their SMI
14 regions of their molecules, that results in this loss that you see happening.
15 And we submitted the Stoler reference as well that corroborates that further.
16 I just wanted to point out that I have not been able to find any rebuttal on
17 that or even anything addressing it. So the same outcome is warranted here.

18 With that, whatever time's left, so save for response. Thank you.

19 JUDGE MITCHELL: Thank you. When you're ready.

20 MR. HOLMAN: Thank you, Your Honor. I'd like to address a few
21 points that counsel for Patent Owner raised in their opening presentation.

22 The first relates to molecular barcodes. We spent some time
23 discussing that in our opening presentation today. It's important to
24 understand where Patent Owner's argument is grounded about the alpha and
25 the beta SMI sequences in Schmitt and how those are the molecular
26 barcodes. If you look at the deposition transcripts that the Patent Owner

1 uses in supporting their arguments, you can see that counsel for Patent
2 Owner was asking Dr. Spellman in this proceeding about Figure 1 in
3 Schmitt, the Schmitt reference. And Figure 1 actually, if we can turn to
4 Petitioner's Slide 14 for a visual on this. So this is an excerpt of Figure 1.

5 So Dr. Spellman and Dr. Satija in the other proceeding were looking
6 at this figure and they were being asked where are the molecular barcodes in
7 this figure. But this embodiment in Schmitt is where the alpha and beta are
8 the only things that are used as molecular barcodes. For example in
9 Schmitt's 12-mer embodiment the alpha and beta SMI tag may be the only
10 molecular barcode. And so that's where the counsel for Patent Owner is
11 asking the witnesses about, and they use that to try and create this argument
12 that in the hybrid tag only the combination of the 3-mer and the fragment
13 end is the molecular barcode.

14 But if you look at the language of the claims, the Claim 1 does not
15 require that a molecular barcode uniquely identify the molecule. So they can
16 be combined with other sequences to, you know, be used in this function for
17 tracking the strands. After all, both Schmitt and the 306 Patent use the
18 barcodes on each end to identify the molecules. The barcodes are combined
19 to form these tags.

20 JUDGE VALEK: Counsel, what about Patent Owner's argument that
21 the language in the Claim Element 1B where it says the duplex tags are
22 attached to both ends of the cfDNA molecule, their argument that that
23 language indicates that the duplex tag can't actually be any portion of the
24 cfDNA molecule because the two things are distinct, duplex tag is a distinct
25 structure from cfDNA molecule?

1 MR. HOLMAN: Yeah. So in that case the Schmitt's 3-mer tag,
2 which, if you're just looking at the adaptor and the n-mer only, that's the
3 exogenous piece. That is a duplex tag, right. That washer adaptor and 3-
4 mer on each end differently label the top strand and the bottom strand on its
5 face, you can see that. And as the Petition referred to, and I think you
6 pointed this out, Judge Valek, that we didn't just refer to this 3-mer as a
7 molecular barcode once, the Petition refers to this 3-mer as a molecular
8 barcode on Page 28, which you noted, Judge Valek, but also Pages 8, 9, 35,
9 38, 40, 53. So it's very clear that the Petition is referring to the 3-mer as the
10 molecular barcode and this exogenous piece, the adaptor plus the 3-mer,
11 that's a duplex tag, it's exogenous and it has a barcode and it meets this
12 requirement.

13 JUDGE VALEK: But, counsel, in follow up on that it also seems like
14 you in the Petition are saying that the duplex tag comprises both the
15 endogenous n sequence and the 3-mer tag. So the molecular barcode is a 3-
16 mer tag, I'll give you that, that's on Page 28. But on 27 you say that the
17 duplex tags comprise both the endogenous and the 3-mer. And if what
18 you're mapping to the duplex tag is the combination of the two things,
19 doesn't the claim seem to distinguish between the duplex tag and the DNA
20 fragment such that you can't be attaching the duplex tag if in fact that duplex
21 tag is part of the DNA already, it's already there.

22 MR. HOLMAN: Well, so the Petition explained that Schmitt's hybrid
23 tags are used to distinguish these strands, so they're used in this process of
24 duplex tagging. But the structure itself of just the 3-mer still constitutes the
25 procedure for duplex tag under the claim language, it's exogenous and it has
26 this barcode. The barcode's used to attract strands, it's not an index barcode

1 and so therefore under that framework or that context, that's why the 3-mer
2 tag is also considered a duplex tag.

3 JUDGE VALEK: Is there a portion of the Petition you can refer us to
4 where you say that the duplex tag is just the 3-mer, where you map just the
5 3-mer to the duplex tag, not the molecular barcode, but the duplex tag
6 specifically?

7 MR. HOLMAN: Well the Petition discusses the tagging step in Pages
8 26 to 27 and there's some extended discussion, Pages 28 through 29. So I
9 would direct the Board's attention to Petitioner's briefing there.

10 JUDGE VALEK: Anything outside of that?

11 MR. HOLMAN: Well there's additional discussion of tagging in
12 reference to Claim 17, which is similar language, that's in the Petition at
13 Pages 40 to 41, or 39 to 41, excuse me.

14 JUDGE VALEK: And is there anything there where you say that the
15 duplex tag comprises just the 3-mer?

16 MR. HOLMAN: I'm not aware that the Petition explicitly said that
17 but that's the position that Petitioner set forth in the Petition is that this
18 duplex tag is an endogenous adaptor with the 3-mer so it's still going to
19 meet this criteria for the Claim 1's tagging step. Now the other aspect -

20 JUDGE HULSE: Could you, I'm looking at Slide 12 of Patent
21 Owner's slides, and this is the deposition transcript of Dr. Satija from the, I
22 believe it's the 817 case. Could you address his testimony that he uses the
23 term interchangeably, molecular barcode with SMRI, UMRI, all of those
24 types of things to indicate that it would be a unique identifier?

25 MR. HOLMAN: Sure, Your Honor. So we don't disagree, Petitioner
26 doesn't disagree that the term SMI or Single Molecular Identifier, or UMI,

1 Unique Molecular Identifier, we don't disagree that those terms can be
2 molecular barcodes. We don't dispute that. But what we're pointing out
3 here is that that's not the only molecular barcode in this hybrid tag
4 embodiment based on the claim language, which doesn't require that the
5 molecular barcode be this complete sequence. It doesn't require that the
6 molecular barcode uniquely identify the molecules. So with that framework,
7 the 3-mer is a molecular barcode but the combination of the 3-mer and the
8 fragment ends, which is, you know, just this SMI or UMI, is also used as a
9 molecular barcode, can be considered a molecular barcode. It's not the only
10 molecular barcode. I think that's one of the things that Patent Owner argues
11 is that the molecular barcode in Schmitt's methods. There's more than one
12 aspect of molecular barcode in play which Schmitt (inaudible).

13 JUDGE HULSE: And I'm sorry, I think I asked this before, but just
14 to reconfirm. In the claim, to reduce and track the redundancy in Step E
15 there, that duplex tag, to satisfy that limitation, has to include the
16 endogenous sequence, right, in order to do that part of the claim in Schmitt?

17 MR. HOLMAN: If you're practicing Schmitt's hybrid method, then
18 yes, the reducing or tracking redundancy will use the sheared ends as well,
19 combined with the n-mer tag. Of course the different, the other
20 embodiments, like the 12-mer tag would not use the fragment end, it would
21 only use the 12-mer part of it.

22 JUDGE HULSE: Right. So then the duplex tag of Step E includes
23 the endogenous tag or endogenous end, right?

24 MR. HOLMAN: So the duplex tag, so Step E is just reducing or
25 tracking redundancy in sequence reads. Actually, let me pull the claim
26 language up. I just want to make sure I'm looking at the right language here.

1 Great. So, yeah, so Step E is reducing or tracking redundancy of the
2 plurality of sequence reads and it's determining distinct molecules based on
3 the paired reads and unpaired reads. And then there's this mapping step.

4 JUDGE HULSE: You skipped over the part about the set of sequence
5 reads using at least sequencing information from the molecular barcodes of
6 the duplex tags to determine the distinct cfDNA molecules. So that duplex
7 tag is the same, has to be the same duplex tag that's referred to in Step B,
8 right?

9 MR. HOLMAN: Correct. That's correct and I apologize for just
10 overlooked that part of the claim. But you can see actually it's quite clear
11 from this language that it says it's, you know, reducing or tracking
12 redundancy of these sequence reads, using sequencing information from the
13 molecular barcodes, actually using at least sequencing information from the
14 molecular barcodes of the duplex tags to determine distinct molecules.

15 So in Schmitt's method, if we're using the sequencing information,
16 even from just the 3-mer, that's, you know, the molecular barcode in
17 determining the distinct molecules. Schmitt also uses in addition to that, it's
18 using the fragment ends in Schmitt's reducing or tracking redundancy
19 processes for that reason.

20 JUDGE HULSE: So you're referring to those as a different molecular
21 barcode?

22 MR. HOLMAN: Different from the 3-mer by itself? Yes, that's one
23 way to look at it, Your Honor. You know, Schmitt refers to them as unique
24 molecule identifiers, so that's the combination of the n-mer and the fragment
25 ends is what's used to uniquely identify molecules, but the 3-mer itself is
26 also a molecular barcode. And so that duplex tag which Judge Valek was

1 asking about, that duplex tag is exogenous adaptor with a 3-mer in it, that's
2 the same duplex tag that's here that's being used, and then they're using the
3 sequencing information at least from, at least sequencing information from
4 the molecular barcode for the duplex tag.

5 JUDGE HULSE: Thank you.

6 MR. HOLMAN: Sure.

7 JUDGE VALEK: So the duplex, just to follow up, so the duplex tag
8 in Claim Element 1B is the same as the duplex tag in Claim Element 1E,
9 correct?

10 MR. HOLMAN: Yes, Your Honor, that's correct.

11 JUDGE VALEK: And in element 1B that duplex tag would have to
12 be the combination of the 3-mer and the endogenous end, for the hybrid
13 methodology?

14 MR. HOLMAN: Well in Schmitt's hybrid methodology that's what's
15 used to track and, you know, perform this process. But the tag itself, the 3-
16 mer and the adaptor, still differently labels the top strand and the bottom
17 strand. Even if you don't look at the sheared ends, there is a difference in
18 that because of the asymmetry of the adaptor in the tags.

19 JUDGE VALEK: That may be, counsel, but what about all the other
20 claim language. Doesn't the claim language require that you use it to
21 identify the distinct cfDNA molecules. As I understand it from your
22 description of how that methodology works, you can't do that unless there's
23 some unique identification, the only way you get the unique identification is
24 the combination of both the end and the 3-mer, correct?

25 MR. HOLMAN: That is correct. But I'd also point out to the Board
26 that the claim language says using at least sequence in the information from

1 the molecular barcodes to the duplex tags, right. So that's met by Schmitt's
2 3-mer alone. And then you add in the fragment ends, which are not
3 excluded by this claimed method, and that's how Schmitt determines the
4 distinct molecules in its hybrid tag method.

5 Briefly I'd just like to touch on the definition of the duplex tag. If we
6 can turn to Petitioner's Slide 12, we have that language from the 306 Patent.
7 And counsel for Patent Owner mentioned that the sentence begins with "For
8 example." And it's true, but I just wanted to point out that this section of the
9 patent, this is the entire tagging section, that's in Column 17, Line 8 through
10 Column 23, Line 20, so there's this long section of discussion of tagging.

11 And so it's talking about different types of tagging. And you can see
12 it here even from this limited excerpt, that patent says polynucleotides
13 disclosed herein can be tagged. And then it says, "For example they can be
14 tagged with duplex tags." So the for example is referring to an example of
15 tagging. And that example of tagging is, in this case, using duplex tags.
16 And then it goes on to explain what duplex tags are.

17 There was some discussion in Patent Owner's portion of the talk
18 regarding the term "reads," and that reads can mean raw sequence reads and
19 reads can mean consensus sequence reads. And I just want to point out that
20 this is indeed consistent with the language and disclosures in the 306 Patent.
21 Figure 1 has been mentioned several times today, but there's also some
22 additional examples that Petitioner cites in its briefing, such as Exhibit 1001,
23 so it's the patent, Column 34, Lines 30 to 35. And we read in that passage
24 the patent refers to reads as discussing consensus sequence reads. And if
25 you keep reading Column 34, Lines 36 to 42, the patent again refers to reads,
26 but now it's referring to the raw sequence reads.

1 In Schmitt itself uses this terminology as well. If you look for
2 example in Schmitt, Exhibit 1083, Paragraph 60, that enumerated workflow
3 overview, the early step, Step 1 for example, mentions discard the reads.
4 That's referring to the raw sequence reads. And then further down in Step 7,
5 there's a mention of collapsing to consensus reads, okay, so that's clearly
6 referring to consensus reads. But then the very next step, Step 8, says for
7 each read, and then refers to grouping requires. And that's using the term
8 read to refer to consensus sequence reads.

9 So there is this terminology in the art that, or understanding in the art,
10 that reads can be kind of the same sequence reads and consensus sequence
11 reads. And the loose language in the patent is really consistent with that.

12 One other aspect that came up previously was the sensitivity of
13 Schmitt's hybrid tag method. Patent Owner argues that there's no data or
14 understanding that Schmitt's hybrid tag method would be sensitive enough,
15 and that it would work. And as Petitioner explained, you know, a person of
16 ordinary skill in the art, they're reading Schmitt, right, and so they
17 understand that Schmitt says we have this method, this duplex sequencing
18 method, it's extremely sensitive, unprecedented in sensitivity actually, it
19 uses those words. And you can do it in different ways. You can do this, you
20 know, this 12-mer embodiment, for example, you can do a hybrid tag
21 method for example, or you can do a sheared ends only method, right. So
22 Schmitt has different embodiments in different ways. But Schmitt says that
23 these ways work and that these methods are sensitive. So a person of
24 ordinary skill in the art reading Schmitt, they don't need to know that
25 Schmitt's 3-mer hybrid tag, they don't need to see data that it's sensitive,

1 they only need to have this reasonable expectation of success when
2 modifying Narayan with Schmitt.

3 Two final points I'd like to briefly make. And that is regarding the
4 allegation from Patent Owner that Schmitt's hybrid tag is, I believe they
5 used the term error prone. And actually we have a couple of slides on this, if
6 you could turn to Slide 75, Petitioner's Slide 75.

7 So Patent Owner points to this disclosure in Schmitt in the top box,
8 this is from Paragraph 60, where Schmitt discusses the process and this
9 analysis portion of the first four nucleotides on the ends following the
10 adaptor, on the ends of the DNA fragment were removed to the propensity
11 for ligation and end repair errors. But as Petitioner explained in Reply, this
12 disclosure in Schmitt, which actually is referring to is in the 12-mer
13 embodiment, but this disclosure in Schmitt is actually an explanation of how
14 to mitigate any potential errors, it's a ligation or end repair spots in these
15 DNA molecules. So removing four nucleotides from the fragment end
16 doesn't obliterate the hybrid tag method, it's actually a way to mitigate any
17 potential errors from the ends.

18 The other part of this argument is the limited spacing requirement.
19 And as Petitioner explained in its Reply briefing, that those arguments
20 simply don't have merit because they are routine methods of dealing with
21 one phase, and this was not an insurmountable barrier that we're going to
22 enter closely.

23 So I see I'm out of time. Unless the Board has any specific questions,
24 I'll take my seat.

1 JUDGE HULSE: I have one quick question. Patent Owner was a bit
2 hesitant to talk about the construction of molecular barcodes and duplex
3 tags. What is your response to that?

4 MR. HOLMAN: Well, so Petition didn't set forth that these terms
5 need specific construction, right? So Petition said these terms should be
6 given their plain and ordinary meaning. And what is plain and ordinary
7 meaning? That's the, you know, based on the language of the claims in the
8 specification in the file history. That's very clear from Phillips and, you
9 know, all the other case law, the classic case law on claim construction.

10 And so our view is that based on the claim language and the
11 specification, and particularly, these terms should be construed as, you
12 know, the duplex tag should be construed as the, you know, the concluding
13 Schmitt's 3-mer tag. Does that answer your question, Judge Hulse?

14 JUDGE HULSE: Yeah, I guess so. It does seem like a lot of this is
15 going to come down to what molecular barcode means, and it doesn't feel
16 like, would you say that that was sufficiently briefed in your papers as to
17 what that means?

18 MR. HOLMAN: Well we do discuss what a molecular barcode is,
19 you know, that's in the Petition, for example Page 3, and the Spellman
20 Declaration also discusses in Paragraph 41. And so based on that, and that's
21 the reference when we discussed generic, which is used to label and track
22 molecules. So I think it is briefed in the Petition materials. And based on
23 the briefing and, again, in view of the patent's claim language and
24 specification, it includes a 3-mer molecular barcode.

25 JUDGE HULSE: Thank you.

26 JUDGE MITCHELL: Thank you.

1 MR. ROSATO: I'll just take a minute here for a few quick points.
2 One on the sensitivity issue, I did want to point out that there was a
3 comment about sensitivity being potentially increased by making use of
4 targeted enrichment protocols. Example 1 actually does use shear select
5 targeted enrichment, so that, I would say it is probably the high-water mark
6 of Schmitt is what we see in Example 1 because it does include these
7 mitigation techniques that Petitioner had referred to.

8 Second, I will thank Judge Hulse for already addressing another point
9 I wanted to make, which was to point to Dr. Satija's testimony. Because he
10 does talk about the term UMI and molecular barcode being used
11 interchangeably. And that's important in the context of what's being cited,
12 which is this one sentence about a hybrid embodiment at Paragraph 30 of the
13 provisional where it refers to the combination. It doesn't even use the term
14 barcode, it uses the term, the combination forms the unique molecular
15 identifier, which, yes, we agree that is the like the barcode and that's what
16 Dr. Satija was testifying about in his deposition.

17 On the phasing issue, we addressed this in the briefing, but their
18 argument in response to that was that there were known techniques to
19 mitigate the phasing issue. Two points on that. In the Kennedy reference,
20 Kennedy doesn't say that be careful of this phasing issue and take mitigation
21 techniques, it states these tags less than 12 nucleotides are incompatible with
22 the known sequencer. So there's no ambiguity there, and that's being
23 recorded in Kennedy. And they did cite to, in their briefing they cited to
24 these papers that allegedly provide mitigating techniques. And they're all
25 papers that predated the Kennedy paper. So they don't explain why the
26 Kennedy authors, which again are the same inventors as the patent, weren't

1 aware of these routine techniques when they wrote what they wrote in the
2 Kennedy paper.

3 Very briefly on claim construction, I mean I don't mean to beat a dead
4 horse, but there is no, there is, at some point Petitioner has to meet their
5 burden on this. If they're going to point to something and say it meets claim
6 language and they seem to now be saying this comes down to some
7 interpretation they want to make, they have to provide an interpretation,
8 construction is necessary for their argument to work. That should be in the
9 Petition materials.

10 Conversely, in the Patent Owner Response, molecular barcodes is
11 addressed in the claim construction stuff. Then it's addressed, albeit to the
12 extent of pointing out agreement as to what is in the cited prior art
13 constituted the molecular barcode. But it is addressed, and then it's
14 addressed extensively throughout the Patent Owner Response briefing. And
15 again, please go look, and I know you will, things rhetorically, but please go
16 look at Petition's Reply brief, and there's nothing in there coming back and
17 saying Patent Owner you're wrong about everything you spent all your time
18 and effort dealing with the Patent Owner Response when it came to what the
19 molecular barcodes are in Schmitt. There's no disagreement on that, right.
20 So take it up here at oral argument they actually, you know, we're going to
21 tell a different story, you know, is not how we want the process to unfold.
22 So that was addressed in the briefing, it was never disputed, and I would ask
23 the Board to take that into account.

24 And absent any further questions, we'll yield. Thank you.

25 JUDGE MITCHELL: Thank you. Well, I want to thank the parties
26 for oral argument, it was very helpful. And I always love it when you're in

1 person because I'm usually here. So thank you so much, and we will take
2 this case under advisement.

3 Thank you. We're adjourned.

4 (Whereupon, the proceedings at 4:26 p.m. were concluded.)

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