

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PACIFIC BIOSCIENCES OF CALIFORNIA, INC.
Petitioner,

v.

THE CHINESE UNIVERSITY OF HONG KONG,
Patent Owner

IPR2024-00028
Patent 11,091,794 B2

Record of Oral Hearing
Held: January 23, 2025

BEFORE: DEBORAH KATZ, MICHAEL J. FITZPATRICK, and
JAMIE T. WISZ, Administrative Patent Judges.

The above-entitled matter came on for hearing on
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teleconference.

IPR2024-00028
Patent 11,091,794 B2

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P R O C E E D I N G S

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JUDGE FITZPATRICK: Good afternoon. This is IPR2024-00028. Petitioner is Pacific Biosciences of California, Inc., and Patent Owner is The Chinese University of Hong Kong. I'm Judge Fitzpatrick. On the line also are Judges Katz and Wisz, and we have a Court Reporter who is going to prepare a transcript of this hearing. We have -- each party is going to have 45 minutes total of argument time. And at this point, I'd like an introduction by Counsel, starting with Petitioner, please.

MR. ROSATO: Thank you, Your Honor. This is Mike Rosato on behalf of Petitioner.

MR. WISE: Your Honor, this is Michael Wise on behalf of the Patent Owner. With me in the room today, I have my partner, Joseph Hamilton, one of our agents, Adeh Vartanian, and my assistant, Calvin Lewis. And also on the call appearing today is my partner, Yingli Wang.

JUDGE FITZPATRICK: Thank you. At the end, we may have -- the Court Reporter may ask you after this is over to spell some of those names. But is there any -- there's no -- I believe there's no protective order. There's no confidential information in this case; is that right?

MR. WISE: That's correct, Your Honor.

MR. ROSATO: Correct.

1

2 JUDGE FITZPATRICK: Okay. Okay. So we don't
3 have any concern with the additional individuals. We do have
4 your demonstratives that each party filed, so we have access to
5 those as PDFs and we can follow along if you just tell us the slide.
6 You're also welcome to use the share function if you want to share
7 it. We can also see it through the virtual hearing software. So
8 with that, we'll turn it over to Mr. Rosato, and why don't you let us
9 know if you want to reserve some time for rebuttal.

10 MR. ROSATO: Yes. Thank you, Your Honor. I'd
11 like to reserve 15 minutes for rebuttal, please.

12 JUDGE FITZPATRICK: Okay.

13 MR. ROSATO: Yeah. And I'm ready when you are.

14 JUDGE FITZPATRICK: Okay. You may proceed.
15 Thank you.

16

17 MR. ROSATO: Thank you, Your Honor. And thank
18 you to the Board and the Counsel present here. I'm going to start
19 on Slide 2. I won't use the share function, if that's okay, but I will
20 refer to the slide number of the demonstrative exhibits. And
21 starting with Slide 2, we'll briefly look at the grounds of challenge
22 here. As the Board is aware, they all involve the Flusberg
23 publications; the Flusberg Paper and the patent, both references
24 from scientists -- the same scientists at Pacific Biosciences, which
25 we'll refer to as PacBio for short, and the PacBio-BAM reference.

1 So each of the grounds involve at least those
2 references and the discussion is going to focus on Claim 1 and
3 Ground 1. All of the '794 patent claims were challenged in the
4 petition. Patent Owner, however, has only advanced argument
5 with respect to Claim 1. The challenge as to the dependent Claims
6 2 through 19 were not separately argued or opposed by Patent
7 Owner, other than their argument for Claim 1, of course. I'm
8 happy to answer any questions on those dependent claims, but
9 absent questions, because those are not challenged, I'll focus on
10 Claim 1.

11 Moving to Slide 3 of the demonstrative exhibits, I
12 want to start with the '794 patent specification itself, and we see
13 how the purported invention is discussed in this specification. It's
14 identified as a method for determining a base modification in a
15 nucleic acid molecule using features derived from a sequencing
16 reaction, and the modifications are determined using a model. And
17 we can unpack these different concepts moving through the
18 specifications, starting with the modification. So those are very
19 broadly described. They're not limited to any particular
20 modification. Several different categories are identified.
21 Oxidation modifications, methylation modifications, examples are
22 given. Even for methylations, there are listed 14 different
23 examples of different types of methylation modifications that can
24 occur.

25 Turning to Slide 4 and looking at some of the other

1 concepts, another concept that's mentioned is sequencing and that's
2 discussed in the specification as well. This specification makes
3 clear that it's not limited to any particular sequencing approach,
4 and it gives several examples of sequencing approaches or
5 sequencing platforms that can be utilized. One identified is the
6 PacBio S-M-R-T, or SMRT Sequencing Platform. Another that's
7 identified is the Oxford Nanopore Sequencing System.

8 As far as the model, that, too, is broadly described. The
9 specification expressly states that any model or data analysis
10 framework is suitable and it outlines broad categories of
11 exemplary types of models that can be used, including machine
12 learning models, statistical models, mathematical models and the
13 like. It's a very broadly described concept and there's very few
14 limits, if any, on what constitutes a model, according to this
15 specification.

16 I'll turn to Slide 5 and we can look at the language of
17 Claim 1. Like the specification, Claim 1 broadly claims a method
18 of detecting a modification in a nucleic acid molecule with no
19 limitation as to the type of modification being detected. And
20 walking through the steps briefly, step A recites receiving data
21 from a sequencing reaction. Step B recites creating an input data
22 structure that has the reaction data and that specifically calls out
23 nucleotide identity position within a window pulsed with an
24 interpulse duration, or IPD.

25 Step C recites inputting the data structure into the model,

1 and then step D recites determining a modification is present using
2 the model. And again, there's no limitation as to the model itself
3 or the type of modification that's being determined. One thing to
4 note with step B is it does not require that any particular reaction
5 data be the determination factor in a modification. The claim
6 simply recites that a modification is detected and it's done so using
7 the model.

8 One other thing to note here is that step B is
9 highlighted with a red box here. That's because this is the only
10 argue -- this is the only element Patent Owner has argued is
11 allegedly missing or a point of distinction from the prior art.
12 That's the only element that's been argued. They're wrong, of
13 course. The prior art teaches or suggests, and therefore renders
14 obvious all aspects of the challenge claims, and we'll see that
15 prima facie case as set forth in the petition materials and it is
16 ultimately un rebutted.

17 I'm going to skip over to Slide 7, please. And sticking
18 with the petition case or starting with the petition case, the petition
19 lays out prior art and expert testimony explaining how the prior art
20 teaches or suggests all aspects of the claim methods, and that starts
21 with the Flusberg publications. Those references disclose
22 sequencing nucleic acid molecules using the PacBio SMRT
23 Sequencing Platform and the reference explains that that
24 sequencing operation generates a pulse trace for each nucleotide,
25 including data for the nucleotide identity, as well as kinetic

1 features, including pulse width, and interpulse duration.

2 The references explain that all of those parameters,
3 sequence information, pulse width, and interpulse duration are all
4 important and used for detecting modifications. And the
5 references discuss and exemplify modeling or using trained models
6 to determine whether a nucleotide in the sequence is methylated in
7 particular or modified as the term is laid out in the '794 claim.

8 Turning to the PacBio-BAM reference, this is a
9 reference that contains the same content that Patent Owner has
10 argued at District Court maps to Claim element 1B and satisfies
11 that claim for purposes of their infringement arguments. PacBio-
12 BAM reference includes the same content that Patent Owner has
13 identified at District Court. This reference discloses a standard
14 data structure in which PacBio SMRT sequencers store data
15 generated during the course of sequencing, and as Patent Owner
16 has already acknowledged, the data structures include identity,
17 position, pulse width, and IPD values for each nucleotide in the
18 sequence. We'll turn to Slide 8, please.

19 JUDGE FITZPATRICK: Mr. Rosato, there was some
20 argument by Patent Owner that you couldn't use -- that a person of
21 ordinary skill in the art couldn't use that format. Does PacBio in
22 their prior art use of SMRT sequencers, does it use a PacBio-BAM
23 as an input data file? Or is it just data that they're acquiring, and
24 then they may process it later?

25 MR. ROSATO: It is the standard format that -- in

1 which the data generated during the course of sequencing is stored.
2 We have -- it is used as input data to modeling and we see that in
3 several prior art references, and I do have discussion points on
4 there I can jump ahead to --

5 JUDGE FITZPATRICK: Yeah. Ultimately, I was
6 wondering if there's, you know -- what's the -- is it ready to go. Is
7 it ready to go kind of off the shelf, the input data, the PacBio-
8 BAM, something that's in that format. Can that just be used as this
9 input data file?

10 MR. ROSATO: It is used in the prior art as an input
11 data structure and we see that in multiple -- the claims don't require
12 that, first of all, but to answer your question, it is -- there are prior
13 art references that specifically talk about taking a PacBio-BAM
14 file as its input and then using the data from that for its
15 downstream analysis. That includes the kineticsTools reference.
16 We also see that in the DeepVariant references, the Wenger
17 reference and the DeepVariant references. DeepVariant is a neural
18 network model and that -- and those references specifically discuss
19 taking the PacBio-BAM file as its input for its use in the neural
20 network.

21 But we'll get -- I'll come back to this. There's a number
22 of problems with this, which have already been dispensed with at
23 the institution stage. Nothing has changed on this point. There's
24 still the problem that Patent Owner doesn't contend with the
25 obviousness case that was advanced. There's also the problem

1 with the argument not being commensurate with the scope of their
2 claims. Their claims don't require any type of parsing or
3 decompression or anything like that, so I think you're touching on
4 a point here, Your Honor, where Patent Owner's rebuttal case
5 really never gets past this BAM file or the obviousness in this case
6 that's been advanced.

7 So I think I was on Slide 8 and, you know, just to sort
8 of run through the prima facie case, we'll touch on rationale to
9 combine. And there's no dispute here as to the specific rationale,
10 the look to the combination of the references here, but there's
11 certainly a logical basis to do so. As indicated, the PacBio -- or
12 excuse me -- the Flusberg publications are discussing detecting
13 modifications using PacBio SMRT sequencing and the PacBio-
14 BAM reference is describing the standard data file that's routinely
15 generated in the ordinary course of SMRT sequencing. Beyond
16 that, all of the references are discussing the claim properties,
17 sequence information, pulse width, interpulse duration, and all of
18 the references are discussing these properties in the context of
19 determining base modifications. There's rationale to combine here,
20 and there's no dispute about that.

21 Turn to Slide 9, please, Your Honor. And I'll briefly
22 highlight the grounds references, as well as content of the grounds
23 references that's pertinent, as well as a few of the many
24 corroborating prior art references that were cited in the petition
25 materials, but we'll start with the Flusberg paper. The Flusberg

1 paper is describing direct detection of DNA methylation without
2 bisulfite sequencing, and doing it using PacBio SMRT sequencing.

3 The Flusberg paper specifically discusses kinetic
4 features, including pulse width and IPD, and describes them as
5 indicative of modification status. It also, like many of the
6 references, describing the importance of sequence information,
7 particularly local sequence context in the context of modification
8 detection and how the sequence information surrounding the
9 nucleotide of interest -- as well as the sequence of the
10 nucleotide of interest -- impacts as an important point of consideration to the kinetic
11 profile. There are experimental examples in the Flusberg paper,
12 including the one shown here in Figure 3 where Flusberg is
13 modeling methylation modifications, is doing so by examining
14 specifically both pulse width and interpulse duration, and is doing
15 so in a window of identified nucleotides. Here the positions
16 identified are 71 through 79.

17 If you can turn to Slide 10, please, and look at the
18 Flusberg patent. The patent, like the publication, is using the
19 reaction data from the PacBio SMRT sequencing operation and
20 using it to detect nucleic acid modifications, including
21 methylations. The reaction data that's specifically called out in the
22 Flusberg patent includes pulse width, interpulse duration, and
23 sequence context, including the identity and positions of
24 nucleotides within a stretch of DNA, and that's even illustrated
25 right up front in Figure 2 of Flusberg, shown here on Slide 10,

1 which regards specifically calling out key reaction data, including
2 pulse width, IPD, nucleotide identity, a stretch of DNA, and
3 highlighting importance to consider the context along the stretch of
4 DNA.

5 We'll turn to Slide 11. I have one more comment on
6 the Flusberg patent and that is the Flusberg patent provides
7 discussion of its classified -- of using a classifier model.
8 Description of a classifier model includes description of various
9 classification algorithms. Those include, a couple to highlight,
10 regression algorithms, and specifically, it's even calling out neural
11 networks, which comes up to some degree in the secondary
12 consideration arguments.

13 We'll turn to Slide 12. Again, we've already talked
14 about the BAM file, but briefly, the content of the BAM file,
15 again, none of this is in dispute. It's a data structure, it contains
16 identity, position, pulse width, IPD values for each nucleotide in a
17 sequence, all of the features that are called out in the claims and
18 the reference even indicates that these features are storage for
19 downstream base modification.

20 Turn to Slide 13. I don't have time to go through
21 every reference, but as explained by Dr. Dessimoz, it's not just
22 Flusberg and BAM. There are numerous prior art references that
23 corroborate the obviousness. What we repeatedly see in the
24 scientific literature is discussion of the importance of considering
25 data, including sequence information, pulse width, and IPD,

1 specifically for base modification detection, and many of these
2 references even cite back to the Flusberg references.

3 Several prior art references, in addition, also specifically
4 discuss using the PacBio-BAM file as an input data structure
5 towards downstream analysis, and this is one of the points that you
6 raised, Your Honor. I'll flip through these very quickly. Again, I
7 don't have time to go through every one of them. I only have time
8 to go through the -- a few examples, but a few are worth
9 highlighting and came up during the briefing.

10 The first one is on Slide 14. That's the PacBio White
11 Paper. Like many of the other references, there's another reference
12 discussing the importance of sequence information over a window
13 spanning a modified base and the impact or interrelation between
14 sequence information and the kinetic parameters of pulse width
15 and IPD, specifically.

16 Turning to Slide 15, the Clark reference is another
17 corroborating reference. This Clark discusses PacBio SMRT
18 sequencing and is specifically identifying, like many of the other
19 references, pulse width and interpulse duration as what it calls
20 principal pulse metrics for modification detection. It even
21 illustrates detecting modifications based on both, pulse width and
22 IPD values, around a window of specifically identified nucleotides,
23 and that's illustrated here on Slide 15.

24 Turning to Slide 16. Again, just, you know, I'm going to
25 briefly move through this prior art. We can return to it, but

1 another corroborating reference that I mentioned is the
2 kineticsTools reference. This is a reference that's discussing taking
3 a PacBio-BAM file as the input data structure and using the data
4 from the BAM file, specifically to query a trained model for
5 modification detection.

6 Turning to Slide 17, there's one more reference,
7 corroborating prior art reference to highlight. This is the Tahir
8 reference. It's another reference that takes reaction data from a
9 sequencing operation. This time, feeding it into a convolutional
10 neural network for modification detection. This reference is worth
11 highlighting for a couple reasons. One, it's yet another reference
12 that's specifically using sequencing information for modification
13 identification, but it's also using the exact same convolutional
14 neural network, this Keras convolutional neural network, that
15 Patent Owner points to as being used in the Tse paper. So Tse is
16 using the exam same prior art convolutional neural network that
17 was already used in the prior art for modification detection.

18 So in sum, the petition presents a strong prima facie case
19 of obviousness. It's corroborated by multiple prior art references,
20 and Patent Owner has not rebutted that case, and we'll look at the
21 rebuttal arguments as we move to Slide 18, please. And as I
22 indicated previously, Patent Owner's only advanced argument with
23 respect to Claim 1, there is no argument, no separate argument,
24 that is, with respect to Claims -- dependent Claims 2 through 19.
25 There's no claim construction argument advanced, certainly no

1 claim construction that would offer a point of distinction. Patent
2 Owner only disputes Claim 1 and with respect to Claim 1, is only
3 disputing step B, the input data structure, and that's illustrated here
4 on the slide with reference to the Patent Owner response, which
5 makes this clear. So we're really talking about the input data
6 structure.

7 And the Patent Owner advances two arguments why they
8 think that this is not in the art -- not in the prior art. The first
9 argument is they argue that prior art actually taught away from
10 using nucleotide identity and they argue that the prior art actually
11 avoided using it all together. Their other argument goes to pulse
12 width. They argue that the prior art actually taught away from
13 pulse width.

14 None of those arguments are credible or substantiated.
15 They don't -- we'll move through the materials, but what we see is
16 not a single reference, a single prior art reference, that actually
17 disparages any of these parameters or supports a teaching away
18 argument. You see the prior art uniformly pointing to the
19 importance of sequence information, as well as kinetic -- both
20 kinetic parameters, and even using pulse width. Not a single prior
21 art reference supports the teaching away argument. There's also --

22 JUDGE FITZPATRICK: Mr. Rosato?

23 MR. ROSATO: Yes, sir.

24 JUDGE FITZPATRICK: I'm sure you'll get to it, but I
25 want to kind of let you know, for the nucleotide identity argument,

1 I know it's not your argument, it's their argument, but I don't -- I
2 didn't fully understand it. It seems to me there's a dispute between
3 -- Patent Owner is saying in the prior art, they're using nucleotide
4 identity, but they're keeping it constant. They're not using it as a
5 variable and that in that, you know, implicitly in that argument is
6 that you need to use it as a variable. I am not following that
7 argument. How would anyone -- if you're doing single molecule
8 real-time sequencing, how would you keep the nucleotide identity
9 constant? I would think that you are -- it's being dictated by
10 whatever you're sequencing.

11 MR. ROSATO: I agree with that in all points of that. I
12 don't think their argument makes sense either. They try to seize on
13 this word of constant. I think what they're getting at is they look at
14 one of the -- the proof of concept experiments in Flusberg where,
15 you know, Flusberg was demonstrating, you know, they're
16 teaching that all these parameters are important and indicative of
17 modification presence, and they want to -- they offer a simple --
18 one of the experiments -- not all of them, but one of them, they -- I
19 think the idea is Flusberg wants to prove that they can reliably
20 detect a modification, so they take two molecules with identical
21 sequences, they know one of them has a modification and the other
22 one doesn't, they sequence both of them, examine them, and say,
23 see, we can reliably predict.

24 So I think Patent Owner seizes on that and says, ah-ha,
25 like they kept the sequence constant so therefore, they somehow

1 don't want to look at it. It doesn't make sense. We went through
2 this with their expert and said -- well, again, first of all, you're
3 arguing this in the context of saying that sequence information isn't
4 even considered. That's not consistent with the broad teachings of
5 the references. It's not even consistent with the one proof of
6 concept experiment you've pointed to because when they're
7 analyzing that, they're doing these alignment operations which are
8 based on nucleotide identity, so they're still using it. It doesn't
9 make sense.

10 I think the other aspect that, you know -- where their
11 argument goes sideways is they tend to look at their claim as if it's
12 a convolutional neural network, which it's not. The model is not
13 limited to a convolutional neural network and I think they seem to
14 envision this scenario where a convolutional network requires
15 specific, you know, inputs or something and it's reviewing it that
16 way and then comparing a single proof of concept experiment to a
17 convolutional neural network, of which their claim is not limited,
18 of course.

19 So I don't think the argument makes any sense. I think
20 it's nonsensical in the context a sequencing operation. We are
21 specifically taking an unknown molecule and sequencing it, and
22 you want to determine both the sequence and an epigenetic
23 modification, like a methylation. It wouldn't -- it makes no logical
24 sense why someone would strip out some of the key information
25 and sequence identity before there's a downstream analysis. So I

1 don't think that argument makes any sense whatsoever.

2 And it also ignores, you know, it ignores a lot of prior
3 art, like the, you know -- many pieces of prior art, which are
4 specifically taking sequence information and using it as a
5 parameter, like the Tahir reference, and like all of the Oxford
6 nanopore references, which they sort of hand wave away. They
7 admit they use nucleotide information and sort of hand wave them
8 away on an argument that they're not within the scope of the claim.
9 They're still relevant to obviousness. So I don't think the obvious
10 makes sense, and I think one of the key problems that we see
11 recurring with any of their arguments is they don't match what's in
12 the prior art, right? They simply don't -- they're not consistent with
13 what the prior art says, and that ultimately is the driver here.

14 I mentioned that -- we'll get to their secondary
15 considerations arguments. Those are interesting, as well. I'll start,
16 if it's okay, we'll just touch on the BAM file. We talked about this
17 a little bit earlier, but I'm now looking at Slide 20. I don't think
18 their missing element argument ever survives the BAM file for a
19 couple of reasons. Their only argument -- again, they've already
20 pointed to the same content in District Court and said, yes, this is a
21 data file and yes, it includes all the features of our claim.

22 They try to back away from that a bit here and argue that
23 well, okay, it's a data structure that has all those features, but it's
24 not necessarily an input. And the basis of arguing that is they
25 point to two things. One, a BAM file comes in compressed

1 format, and two, it has some data beyond the claim recited
2 features, so it'd need to -- there'd need to be a parsing operation
3 that took place. And again, as this all sounds familiar, it's the
4 exact same argument that was advanced at the institution stage. It
5 fails for the same reason it was rejected there.

6 You know, that's not consistent with what they've argued
7 at District Court, and it also treats steps like -- routine steps like
8 depressing and parsing data as if there is somehow a challenge
9 when they were not. It also erroneously views a person of
10 ordinary skill as someone who would mindlessly or thoughtlessly
11 do things to sabotage utility, which we know as a matter of law, a
12 person of ordinary skill does not do. So none of that has changed
13 and the record has only gotten worse on that point we see that as
14 we turn to Slide 21.

15 Dr. Dessimoz was asked about this during cross-
16 examination. They tried to gain some ground with him and he
17 rejected those arguments. He explained that decompression,
18 parsing, those are very straightforward operations, very trivial
19 steps. They're routine for a person of ordinary skill in the art.
20 That's all true and it corroborates one of the bases the Court
21 rejected this argument the first time around.

22 If we turn to Slide 22 -- I mentioned this earlier -- but it's
23 not just Dr. Dessimoz's testimony that obviously is valuable
24 evidence, but it's also corroborated by the prior art. There are
25 multiple references that discuss taking a PacBio-BAM file as the

1 input and using that for downstream analysis, including
2 modification detection. And as I mentioned earlier, that includes
3 the kineticsTools reference, which expressly identifies the PacBio-
4 BAM file as its input, as well as the Wenger and DeepVariant
5 references, which are, you know -- DeepVariant, again, is a neural
6 network model and DeepVariant expressly takes, as its input, reads
7 in the BAM format.

8 And I'll turn back to Slide 19. I mentioned this. I
9 appreciate you bringing it up earlier, Your Honor, because I do
10 think it's an important point that really cuts the legs out from any
11 rebuttal argument here. But the other problem with this argument
12 about decompression and parsing, like many of the arguments that
13 are advanced, are just not commensurate with the scope of the
14 plan. But instead the step B, which is being argued here uses the
15 open-ended comprising language. It doesn't recite 'consisting of',
16 so ultimately, this idea of additional data possibly needing to be
17 parsed out is irrelevant given the scope of these claims.

18 The claim also doesn't say anything about decompressing
19 data or required data come in compressed, decompressed, or some
20 other format. It's just data. As -- and this was all confirmed by
21 their expert, Dr. Koo, during cross-examination. We asked him
22 what a data structure is and he said that in computer science, that's
23 simply an object that contains information. He confirmed the
24 claims are open-ended and there's nothing about compression or
25 decompression.

1 So this argument can be rejected for a number of reasons,
2 one of which is the scope of its claims and the disconnect there. I
3 want to -- I'll get back -- we talked about the teaching away from
4 nucleotide identity argument. Again, I agree. I don't think this is
5 an argument that particularly makes sense. It's also not
6 corroborated or consistent with the disclosure in the references,
7 and that includes the Flusberg publications, which are specifically
8 calling out for their reaction data sequence information, and even
9 illustrating that in Figure 2.

10 And Flusberg publications, like many of the prior art
11 publications, are specifically emphasizing the importance of local
12 sequence information during modification analysis and the impact
13 that has on kinetic signatures. So it's hard to say when multiple
14 prior art references are calling this out in the context of sequencing
15 operations, that they somehow teach away from nucleotide
16 identity. They don't. That's just not true.

17 We'll turn to Slide 24. Again, I touched on this, but even
18 in this simple, you know, this proof of concept experience that
19 Patent Owner seizes on to say, oh look, they knew what the
20 sequence was ahead of time and they controlled for it, it still
21 doesn't make sense to say that nucleotide identity was excluded
22 and it's indefensible in view of the disclosure there, which takes
23 the sequence information and then as part of its modification
24 analysis is conducting sequence alignment operations as part of
25 this proof of concept.

1 We asked Dr. Koo about this during cross-examination.
2 We can look at Slide 25. He confirmed the obvious here, which is
3 yes, you cannot possibly do a nucleotide sequence alignment if
4 you don't know the sequence information or the nucleotide
5 identity. He agreed with that and beyond that, had no good reason,
6 you know, why one would say that nucleotide information is
7 somehow not included here other than to sort of dismiss these
8 examples what he considered not real data, which of course is
9 false, as well. That seemed to be just a misapprehension by Dr.
10 Koo there. The specification specifically calls it out as real data,
11 and it wouldn't matter even if it was prophetic. So there's no good
12 justification for this teaching away argument. We'll turn to Slide
13 26. Now --

14 JUDGE FITZPATRICK: Mr. Rosato? I --

15 MR. ROSATO: Yes.

16 JUDGE FITZPATRICK: -- apologize. I should've
17 mentioned this earlier. You're about 32 minutes into your
18 presentation. Did you ask for 15?

19 MR. ROSATO: I asked for 15. Yeah, yeah. So --

20 JUDGE FITZPATRICK: Now you have 13.

21 MR. ROSATO: -- let me -- I'll get through --

22 JUDGE FITZPATRICK: So --

23 MR. ROSATO: -- a couple -- right. I'll use a couple
24 more minutes so we can move past the nucleotide identity. I think
25 that's not a credible argument. I'll turn to Slide 28 and briefly

1 address the pulse width -- teaching away from pulse width
2 argument. Again, this is not a credible argument. There's not a
3 single reference identified that says anything negative about pulse
4 width and certainly not something that would amount to a prior art
5 teaching away. We've got the Flusberg references that are
6 repeatedly emphasizing the importance of pulse width and its
7 usefulness and modification detection.

8 And as we see on Slide 9, it's not just the Flusberg
9 references and the BAM file, as well, but we see this with multiple
10 corroborating references like the Clark reference that's specifically
11 identifying pulse width, in addition to IPD as principal pulse
12 metrics considered in modification analysis and even giving
13 examples of detecting modifications with both pulse width and
14 IPD.

15 We can skip over to Slide 31, which addresses the Schadt
16 reference. This is -- this really is Patent Owner's main argument
17 about teaching away. They say that Schadt disparages pulse width.
18 It does no such thing, as stated plainly in the same portion of
19 Schadt and confirmed by Dr. Dessimoz, Schadt actually states that
20 both, pulse width and IPD, produce reproduceable variations
21 indicative of base modification.

22 So it's actually speaking positively about pulse width.
23 The Schadt paper goes on to explore the parameter of sequence
24 context and explains that it's look -- it's going -- it's studying the
25 interaction between sequence context and IPD, so it looks at that.

1 That is by no means a teaching away. It credits pulse width and
2 then explains that it's going to look at one particular interaction.
3 That is not teaching away.

4 I'll just briefly address the objective indicia and then
5 reserve the rest of time for -- any remaining for rebuttal, but
6 turning to Slide 22, most of the argument here is -- so they point to
7 this Tse paper that used the convolutional neural network and they
8 argue -- they're arguing that Tse supports non-obviousness and
9 then they go on to make arguments about the ability to detect five
10 5mC modifications, avoid bisulfite sequencing.

11 JUDGE FITZPATRICK: Mr. Rosato, to save you a little
12 bit of time, I want to -- I fully understand that the argument that
13 there's no nexus because it's a species -- that their evidence is in
14 relation to a species of Claim 1, specifically the detection of 5mC
15 or 5-Methylcytosine. Let's assume, though, for a second that there
16 is a nexus. Can you speak to the, you know, the evidence in the
17 other regard, as to how probative it is?

18 MR. ROSATO: Sure. I mean, there's another reason
19 that -- even assuming there was nexus to the Tse model, there's a --
20 which obviously we don't agree with -- there's another problem
21 with that, and that is there's nothing in the Tse model that isn't
22 already found in the prior art. And following the prior art, we
23 know as a matter of law is, you know -- is not a basis or
24 undermines the objective -- the value of objective indicia for
25 establishing non-obviousness.

1 So in other words, if something is -- if a model is pointed
2 to and that same model is, you know -- is found in the prior art and
3 rendered obvious, that undermines the strength of any objective
4 indicia and that's certainly the case here. The other problem is
5 they argue accuracy. I mean, that ties to the claim issue. There is
6 no accuracy requirement and there are different models that are in
7 the '794 patent of terrible accuracy and they're within the scope of
8 the claim. So there's no -- they don't -- I would say the accuracy
9 doesn't save them -- saves -- you know, prior art approach doesn't
10 save them either and they never get past nexus.

11 So with that, I'm happy to answer any other questions. I
12 want to save a few minutes for rebuttal, if I may, but I'm willing to
13 do that.

14 JUDGE FITZPATRICK: Okay. Let's -- I've got you
15 down as -- so you've got eight minutes left when you get back up.
16 And we'll turn to Mr. Wise now.

17 MR. WISE: Excuse me, Your Honor. Okay. Can -- I'm
18 Michael Wise, again, for the record. And may I share my
19 presentation?

20 JUDGE FITZPATRICK: Yes, please. Go ahead.

21 MR. WISE: Can I -- I'd like to reserve five minutes for
22 rebuttal please. Okay. Here we are. I'm going to move to Slide 4.
23 This is Claim 1 of the patent. There's four limitations that are
24 relevant here. The first one is limitation A, which is directed to
25 PacBio single molecule real-time sequencing, abbreviated as

1 SMRT sequencing or SMRT sequencing. Limitation A receives --
2 recites receiving data from measuring pulses in an optical signal.
3 That corresponds to PacBio sequencing, the SMRT sequencing.

4 Limitation A also recites that values are obtained from
5 these pulse signals, including pulse width, interpulse duration, the
6 identity of each nucleotide, and the position of the nucleotide
7 within a sample nucleic acid molecule. Pulse width and interpulse
8 duration are measurement kinetics made by SMRT sequencing. So
9 while the patent specification states that it's not limited to a
10 particular single molecule sequencing platform, the limitations of
11 Claim 1 require SMRT sequencing. Now, in District Court, what
12 we argued was the BAM file is the received data in step A and the
13 reason the BAM file is not the data structure in step B, is step B
14 has properties that are not found in the BAM file.

15 So with respect to step B, you create the input data
16 structure from the data that comes from the BAM. You parse that
17 data out and create your input data structure. That input data
18 structure has a window of sequence nucleotides and we're going to
19 talk about how that window has to be identical in the training data,
20 and that's one of the reasons why the BAM file cannot be just a
21 direct input because it has sequenced nucleotides of all different
22 lengths. Also, the BAM file -- the input data structure, again,
23 requires nucleotide identity, which comes off of the BAM file, but
24 it requires you identify the nucleotide relative to a target that
25 you're looking for the modification. That's not in the BAM file as

1 it comes off the sequencer. You have to create that data structure.

2 So the data structure requires you to create a position --

3 JUDGE FITZPATRICK: Mr. Wise? I'm sorry.

4 MR. WISE: Yes.

5 JUDGE FITZPATRICK: I didn't understand that last
6 point. You know what, I just looked at step A here --

7 MR. WISE: Yeah.

8 JUDGE FITZPATRICK: -- which I think you said the
9 BAM file -- the PacBio-BAM file has, you know -- it embodies the
10 data that is received in step A.

11 MR. WISE: That's true. That's true.

12 JUDGE FITZPATRICK: Okay.

13 MR. WISE: And it has other --

14 JUDGE FITZPATRICK: And it has --

15 MR. WISE: It has other data --

16 JUDGE FITZPATRICK: Okay.

17 MR. WISE: -- too that needs to be parsed out.

18 JUDGE FITZPATRICK: Understood.

19 MR. WISE: You parse out the data. We agree that it's
20 well within the scope of -- I'm sorry, Your Honor. You were going
21 to ask --

22 JUDGE FITZPATRICK: Yeah, yeah. No, no, no. I was
23 going to get to a different issue on that. The first two things that
24 are listed are, quote, "an identity of the nucleotide" and then --

25 MR. WISE: That's right.

1 JUDGE FITZPATRICK: -- a position of the nucleotide
2 within the sample nucleic acid molecule. That to me strikes me as
3 embodying what you've just said would be missing and that is --
4 you didn't use the word sequence in the context, but you said
5 something very similar. I forget what you said.

6 MR. WISE: You have to have a target. You have to
7 have a target within the sequence. You have to have a target that
8 you've identified to determine whether or not to modify it, but then
9 you create a window around it. So it requires a daily input
10 structure that's different than the BAM itself. You have to create
11 that data input structure from the BAM or from --

12 JUDGE FITZPATRICK: What's the word --

13 MR. WISE: -- whatever that is --

14 JUDGE FITZPATRICK: Is the word target in Claim 1?

15 MR. WISE: The word target is in Claim 1 in step B. It
16 says, the position -- sorry -- it says, the position of the nucleotide
17 with respect to a target position within the window.

18 JUDGE FITZPATRICK: Target position, okay.

19 MR. WISE: Right? So you've got a window --

20 JUDGE FITZPATRICK: Where is -- okay.

21 MR. WISE: So --

22 JUDGE FITZPATRICK: How do you expect to define
23 target? Because I've just been considering this as, you know --
24 whatever -- like one way to reach this in my mind is whatever
25 particular nucleic, you know, acid you have just detected, that

1 could be -- for example, that could be your target. That could be
2 right in the middle. We're keeping track of the three that we just
3 did right beforehand, and then we're going to have three more
4 coming down the pipe as we're sequencing this. It seems to me
5 that the target could really be anything, but the most natural
6 reading would be why not just pick the one that you are focused on
7 right now. If that's wrong, can you explain that, why I would be
8 wrong?

9 MR. WISE: Well, the BAM file has all the data from all
10 the sequencer reactions in one fell swoop, you know? It just gets
11 thousands and thousands of sequences. You're not looking at the
12 sequences as they come off the sequencer. The data all comes in.
13 It's a giant file with thousands and thousands of sequences of all
14 different lengths, and then you have to take that data and structure
15 it into the model, and that's true of all of the things that they're
16 talking about. It's not an off the shelf solution that you just put it
17 into the program.

18 The program -- you know, you may have something in
19 between the BAM file and the program that parses the data and
20 packages the data so that the program can use it, but you've got
21 millions -- you've got thousands of sequences of varying lengths.
22 And one of the things that all of the experts agree is in step B, you
23 take the same structure. Let's say it's a ten nucleotide window
24 you're looking at and you decide in the middle, I'm going to look
25 to see if that's the modification, and I put in all the positions on

1 either side of it from the nucleotides, what their identity is, what
2 their position is relative to that target, and the pulse within the
3 interpulse duration information.

4 And that same information has to be used to step C to
5 train the model, and you compare modified versus unmodified data
6 sets to be able to train the model, to then be able to, under step D,
7 to determine if a modification is present at that target. Maybe it
8 would be helpful if I show you some figures.

9 JUDGE FITZPATRICK: Can I just say -- if you don't
10 mind going back just real quick, I have one follow-up question.
11 Maybe a way to ask you differently is now I'm focused on step B,
12 the language there --

13 MR. WISE: Yeah.

14 JUDGE FITZPATRICK: -- and in those PacBio-BAM --
15 those reads -- you said there'd be like maybe thousands of reads on
16 there of different lengths, of different poly nucleotides. Let's just
17 say -- let's just pick any one of them, whatever it was -- 100 long.
18 In that data, it has the identity of all 100 nucleotides.

19 MR. WISE: That's correct.

20 JUDGE FITZPATRICK: It also has them in order. So --

21 MR. WISE: That's correct.

22 JUDGE FITZPATRICK: -- doesn't it -- isn't it arbitrary
23 at this point -- I mean, not arbitrary, but you could pick any target.
24 You could say the target is number two. I could tell you --

25 MR. WISE: Yeah.

1 JUDGE FITZPATRICK: -- with -- you know, that
2 there's an adenine that's five down from that, so I feel you could
3 pick any target because you know all the data. So you could pick
4 any target.

5 MR. WISE: You could. But remember, when you train
6 the model to be able to detect the modifications, you have to have
7 the same data structure, the same size window. So let's say you
8 have 50 sequences coming off the -- coming out of the BAM file.
9 One is, you know, 30 nucleotides long, one is 100 nucleotides
10 long, another one is 1,000 nucleotides long. You have to parse up
11 the data into this data structure and train it using the same window
12 and same the properties so that you could make that detection.
13 You just don't read the data on -- you just don't upload the BAM
14 file and it magically does this. You create the input data structure
15 from the BAM data and that's part of the invention. That is the
16 invention and you have to make sure you use that same structure to
17 train. And that's something that both of the experts agree on, but
18 let me just show you a visual. You can see here that you -- that on
19 the left is the training.

20 So you have this data structure, you have a target in the
21 middle, and for every nucleotide, you've got an identity, you've got
22 a position relative to the target, and you have the IPD and PW
23 values. I'm on Slide 5. And on the right is what you do when you
24 do the detection. You have to use the exact same data structure
25 that you've created from the BAM file, from the BAM data, and

1 both experts agree that you must train the model with the same
2 format, the same input data.

3 So the BAM file is the received data from the sequencer.
4 You have to create an input data structure that has those properties.
5 The BAM file doesn't have a target. You have to identify the
6 target, and it's well within the skill in the art to identify a target.
7 I'm not saying identifying a target's novel. It just is -- the BAM is
8 not an off-the-shelf solution that you just plug and play.

9 JUDGE FITZPATRICK: Can I -- doesn't what's shown
10 in paragraph 44 of Koo's declaration, doesn't that also go against
11 you? Because he's acknowledging --

12 MR. WISE: Paragraph 44?

13 JUDGE FITZPATRICK: The person -- I'm sorry, it's on
14 your Slide 6. It looks like it's paragraph 44 --

15 MR. WISE: Okay.

16 JUDGE FITZPATRICK: -- on Exhibit 2041. He's
17 saying --

18 MR. WISE: Okay.

19 JUDGE FITZPATRICK: -- that a person of ordinary
20 skill in the art would understand that to train the model, to detect
21 modifications from an input data structure, the training must be
22 providing the same format, which you go on -- which he goes on to
23 define as including the same window.

24 MR. WISE: That's correct.

25 JUDGE FITZPATRICK: So if a person in the art of skill

1 knows that --

2 MR. WISE: Yes.

3 JUDGE FITZPATRICK: -- then isn't it obvious?

4 MR. WISE: No. You know, and the reason it's not -- I
5 mean, it's -- the reason it's not obvious -- if you look at what's
6 happened in the art, if we look at what the premise of this base is,
7 is that Petitioner argues that the premise of the case is that the
8 plain properties of the input data structure represent nothing
9 beyond the predictable use of known variables according to their
10 purported well-characterized role in base modification detection.
11 And what is that? I'm on Slide 9.

12 If I look at Slide 10, what the purported well-
13 characterized role -- I'm sorry, I'm on Slide 9. The purported well
14 characterized role is you have to consider it. You have to consider
15 it -- consider sequence context in smart sequencing base
16 modification detection.

17 Slide 10, their expert tells you how to do it. How do you
18 consider it? Well, you -- because sequence context affects IPD
19 and PW, context must be controlled for or explicitly evaluated.
20 Slide 11, how do you do that? Well, you look at Flusberg.
21 Flusberg avoids using sequence context as an express input
22 variable because it's held constant. All the sequences in Flusberg
23 are varied in methylation state, not nucleotide sequence. And how
24 does Dr. Dessimoz know that? Well, he knows that because he
25 shows -- he says, you look at the figures, Figures 1 through 4, and

1 they show the same nucleotide sequence with only the
2 modification status varied.

3 Slide -- that was Slide 11. Now, if I go to Slide 12, the
4 Flusberg -- you know, what he's told us -- Dr. Dessimoz told us to
5 avoid using sequence context as an input variable in your input
6 structure and hold it constant. And here in Slide 12, it shows you
7 that in Figure 2, you use identical sequences and you just vary
8 methylation. So you're only looking at the interpulse duration
9 values and you're not looking at the nucleotide sequence at all.
10 That's how you consider it. You hold a constant.

11 Slide 13, here's Figure 4. And now they showed you 1
12 and 3 already. Same thing. Flusberg avoids using sequence
13 context as an input variable because it's held constant. You don't
14 use it in the input data structure, according to Flusberg. You just
15 look at IPD values and this Figure 4 is methylated adenine. Now,
16 on Slide 14 --

17 JUDGE FITZPATRICK: Can I ask you a question about
18 that last slide?

19 MR. WISE: Yeah, certainly.

20 JUDGE FITZPATRICK: I think -- right at the end, I
21 think you said this was methylated what?

22 MR. WISE: This is methylated adenine, MA.

23 JUDGE FITZPATRICK: So they use a string of -- they
24 probably fed it with adenine unmodified and then adenine -- a
25 string of adenine that was methylated, right?

1 MR. WISE: Right. You're comparing methylated versus
2 unmethylated. If you look at the positions in A, the dumbbells on
3 A, this is showing what he's -- what Dessimoz is saying. You
4 eliminate nucleotide identity or sequence context from the input --
5 from the other input by making --

6 JUDGE FITZPATRICK: As a variable. I would correct
7 you. As a variable. Not as an input. Because otherwise, why
8 wouldn't it -- wouldn't it be the exact same? I doubt. The exact
9 same pulse width and IPD that you would get if you did this with
10 cytosine and then methylated cytosine?

11 MR. WISE: No. You're only looking at the IPD values.

12 JUDGE FITZPATRICK: I understand that point. What
13 I'm saying is, is the IPD going to show up -- is there going to be
14 some sort of signature that shows up that is different for, you
15 know, when you're looking at methylated cytosine versus regular
16 cytosine, than looking at methylated thymine --

17 MR. WISE: Well, you're looking for differences in the
18 values on identical templates. So you're agnostic in terms of what
19 the actual thing is, I mean, but then you go back and look at the
20 sequence after you've identified that there is some kind of a
21 variation.

22 JUDGE FITZPATRICK: All I'm getting at is that I
23 believe -- and you can try to -- I would like -- if this is not true, I
24 want you to explain why. I think that the identity of the nucleotide
25 is going to affect what those pulses are going to look like.

1 MR. WISE: Absolutely, they do.

2 JUDGE FITZPATRICK: Okay.

3 MR. WISE: But you don't use nucleotide identity as --
4 you don't use nucleotide variable as part of your input data
5 structure. In Flusberg, you hold a constant.

6 JUDGE FITZPATRICK: I think I understand your
7 argument. I just -- I dispute that because it's constant, it's not --
8 that means that it's not in the input data structure.

9 MR. WISE: But that's the premise of the argument.
10 That's the premise -- they said that in their petition. Their expert
11 has said it, is that, you know, that this is -- that the reason -- it goes
12 back to this original point. They argue this is a variable.
13 Nucleotide identity is a variable that goes into the input data
14 structure and they -- their expert says, no it's not. You hold it
15 constant. That's what you do. That's what you do in all of the
16 references.

17 All the Flusberg references teach the same thing, hold it
18 constant. They never look at the identity as an input, you know, as
19 an input -- as a separate input with values that go into a structured
20 model that allows you to make predictions of methylation state.
21 They hold them constant and that's what Claim 1 is about. You're
22 putting nucleotide identities as values and you're putting their
23 position as values. Maybe I should go back to Claim 1.

24 So right there. You derive the values from the BAM file
25 and then you put those values into a structure that has the identity

1 of the nucleotide -- that's one value -- the position of the nucleotide
2 relative to the target, and then the pulse width and the IPD. And in
3 Flusberg, you don't do that. You hold it constant. It doesn't have
4 a value in the input data structure that's independent.

5 JUDGE FITZPATRICK: Is that true in Flusberg, in
6 your -- Mr. Rosato had said it's only in some of the examples or
7 maybe he said it's only in one specific example.

8 MR. WISE: Their expert says it's all the examples. He
9 says all the examples do that. You know, that --

10 JUDGE FITZPATRICK: Which cite should I be looking
11 at though?

12 MR. WISE: Right here. You know, right here where he
13 says -- right here. Examples 1 through 4. How do you know that
14 Flusberg holds it, you know -- doesn't use it as an input variable?
15 Flusberg holds it constant and his example -- he says, look at 1
16 through 4. So they've showed you 1 to 3, here's number 2.
17 Number 2 says it right there in the legend that the two templates
18 are the same, so you're holding a constant. Same thing here on
19 Figure 4. They're constant. That's what Flusberg does, holds
20 nucleotide identity as a constant, as opposed to putting in of the
21 input data structure as a variable.

22 Slide 14. When we cross-examined their expert, he said,
23 look, we can -- why'd you do this? Well, we can fix sequence
24 context and that's what they did in the Flusberg publication. And I
25 said, is it true in the patent, too? He says, that's right, that's why I

1 refer to them jointly. As far as these statements are concerned, one
2 is -- one is like -- one true for -- one true for the other, right? And
3 then when we look at the patent, it's the same data. All of the
4 examples, all of the experimental examples in the patent, do not
5 use nucleotide identity as a variable in input data structure because
6 they're held constant.

7 And if we look at Figure 16, which is identical to 2C,
8 you can see that there are no nucleotides, just positions, and they're
9 looking at IPD ratios. In Figure 14, which is identical to Figure
10 4C, this is the one that they criticized Dr. Koo for somehow
11 missing. He and Dr. Dessimoz both said that this figure, Figure 4,
12 which is identical to Figure 4C, avoid using nucleotide identity as
13 an input because it's held constant.

14 Now, when you look at the patent, we go to Slide 16,
15 both experts say the '338 patent controls for sequence context by
16 keeping it constant. And to predict base modifications, the '338
17 patent considers a variety of kinetic properties. It says so right
18 here. This is where they talk about using a model to predict base
19 modification. And what are the features that they give you? Do
20 they give you nucleotide identity? No, because they've held it
21 constant. It's not part of the input data structure like in the Lo
22 method. So they give you a set of features and the features are
23 pulse width, pulse duration, pulse height, pulse amplitude
24 variability, but tellingly absent is nucleotide identity or position of
25 the nucleotide relative to the target. It's all anonymous when it

1 comes to the nucleotide because they're not using it in the input
2 data structure.

3 And then if you go to Column 67, they tell you what else
4 it could be. It can be pulse width, branch rate, mismatch rate,
5 deletion rate. Nucleotide identity is nowhere to be found. He said
6 the same thing -- you know, Dr. Koo testified with respect to all
7 the so-called corroborating art, but the same thing is true. They
8 hold nucleotide constant and when you hold it constant, you're not
9 putting it into an input data structure as a variable, which is what
10 Claim 1 is about. Each one of the references -- Clark, Schadt, the
11 White Paper, kineticsTools all hold a constant, and their own
12 expert agrees. Would you agree it's fixed just like the White
13 Paper? I'm talking about kineticsTools. He says, yeah. As the
14 name indicates, it's control in this case and yes, I think it's
15 consistent with the method that is described in the White Paper and
16 the Flusberg publications. It's not used as part of an input data
17 structure.

18 So the well-known use, which is the basis for this -- for
19 the grant and the basis for their argument, was to hold it constant,
20 not to use it as an input variable. Now, the BAM doesn't solve
21 anything. The BAM doesn't tell you how to do anything. The
22 BAM is just the data file, so the Flusberg publications and all the
23 art they address, the use of SMRT sequencing to detect base
24 modification avoiding using nucleotide identity as a property in an
25 input data structure by holding a constant. Now, the BAM tells

1 you nothing about base modification. The BAM is just the
2 received data. The experts agree that BAM does not need to
3 modify --

4 JUDGE FITZPATRICK: So I put -- but will the BAM
5 file tell you whether it was a string of adenines versus a string of
6 thymine or cytosines or --

7 MR. WISE: Yeah. The BAM file has the sequencing
8 data in it.

9 JUDGE FITZPATRICK: Okay. And --

10 MR. WISE: You still have -- you know, alignment is
11 known. Alignment is not the invention. The invention is figuring
12 out what the input data structure would be that would allow you to
13 do base modification prediction. And while Flusberg says, yeah,
14 sequence context is important because it affects IPD and PW,
15 Flusberg says, hold it constant, and the reason they do is because
16 nucleotide identity is a confounder. In other words, it'll make --
17 this comes from their expert -- a person of -- right here at the end
18 on the far right. A person of skill in the art would understand -- on
19 Slide 9 -- a person of skill in the art would understand based on a
20 prior arts recognition that sequence context accounts are 80
21 percent of variants in IPD.

22 You must consider variation or sequence context acts as
23 an uncontrolled confounder that drowns out the signal for
24 methylation in noise, and the way they solve for it is they don't use
25 it in the input data structure the way Lo does, the way Claim 1

1 does. They hold a constant because they can't detect anything with
2 their methods and that never changes. All the Flusberg references
3 do that and the same thing is true with PW. They eliminate PW
4 from the consideration because of the same problem, because
5 between PW and IPD and nucleotide identity all being in the data
6 input structure, they've got all this noise and they can't detect
7 things.

8 So when you get to two thousand -- let's see what I have
9 left. So when you get here, Slide 30, in 2010 and 2011, you have
10 these Flusberg and Clark studies that show you the whole
11 nucleotide identity constant and to measure PW and IPD. In 2012,
12 the White Paper comes out. It doesn't even use the word pulse
13 width. It says, just use IPD. And then in 2013, Schadt publishes
14 and says, don't use IPD -- don't use pulse width because pulse
15 width is not sensitive enough, just use IPD. And the same is true
16 with kineticsTools. It just uses IPD.

17 And in 2019, the PacBio -- Schadt, who is a PacBio
18 employee, publishes the -- another reference that says the same
19 thing, just use IPD ratios. So the well-characterized properties or
20 the well-characterized roles for IPD -- you would use IPD and look
21 at the ratios, you would keep nucleotide identity constant and don't
22 include it as part of the input -- as a variable in the input data
23 structure, which Lo does, and PW is something you don't use.
24 That's what the art taught.

25 JUDGE KATZ: So Mr. Wise --

1 MR. WISE: Yes.

2 JUDGE KATZ: -- if the sequence identity is a constant,
3 so all you're determining is just the modification of a known
4 sequence, I'm kind of confused what the use of that is.

5 MR. WISE: You have -- so okay, so the papers show
6 that you compare identical sequences and then when you go to, for
7 example, kineticsTools -- well, with respect to kineticsTools and
8 the White Paper, the tools that they developed, you would either --
9 you would create two database, two sets of data. You have your
10 sequences that are modified and your sequences that are
11 unmodified, and then you line them up and then you just look at
12 the -- you look at the IPD ratios. So you can either do that with
13 actual sequences that are both, you know, run through the
14 sequencer and then you line them up and then you just look at the
15 ratios, or you can use a lookup table that has all the ratios for IPD
16 for all the different types of sequences that it could be. And you're
17 just looking to see if something is off. You're just looking --
18 you're just comparing them. That's what these tools do.

19 JUDGE KATZ: So you have to have a sequence that's
20 modified and a sequence that's not modified? You're not -- this is
21 not useful for taking a sequence and determining if it is modified
22 or not? Sort of what you just described is that you know there's a
23 sequence that's modified and you know that there's one that's not
24 modified.

25 MR. WISE: Well, the way the tool works, for the White

1 Paper and kineticsTools, if you look at the description of them,
2 they talk about you would -- you have your sample that you want
3 to figure out if it has a DNA modification, and you have to amplify
4 the sample to unmodify all the -- one part -- you take the sample
5 and you split it into two and you amplify one so it becomes
6 unmodified, and then you take your original sample that has
7 modifications, you sequence both of them, you align them, and
8 then you input it into the system and look for it and the system tells
9 you if they're off in terms of the interpulse duration values. Does
10 that make sense?

11 JUDGE KATZ: I suppose, but you're starting off with
12 the knowledge of the modification.

13 MR. WISE: Well, you don't know until -- you don't
14 know if there's a modification until you do the -- until you run
15 the -- until you put it in the program and it looks at the IPD ratios.
16 So if the IPD ratios are off, then there's a modification. If they're
17 not off --

18 JUDGE KATZ: A modification in a location that you
19 knew beforehand?

20 MR. WISE: Yeah. No. No, no. You don't know with
21 these. So in the --

22 JUDGE KATZ: But the sequence identity is constant, so
23 you sort of don't know -- you have to know beforehand what
24 you're looking at, according to what you're saying.

25 MR. WISE: No. No, no. No, no.

1 JUDGE KATZ: Okay.

2 MR. WISE: The nucleotide identity is kept constant in
3 the tools because you use identical sequences, you align them, and
4 then you just look to see if there's a modification based on the IPD
5 ratios. Is it statistically off? So back --

6 JUDGE FITZPATRICK: I'm sorry to interrupt. Could I
7 ask you just a question to clarify what we were --

8 MR. WISE: Yeah.

9 JUDGE FITZPATRICK: -- just talking about. The way
10 I think I understand your position is that in Flusberg, the thing
11 that's analogous to the invention -- although it's not the invention
12 in your position -- is that they're feeding in an input data structure,
13 but it's all going to be -- we'll just use an example -- it's all going to
14 be cytosine, and then they're also feeding in the exact same length
15 of cytosine that's modified. And they're observing the interpulse
16 duration and trying to figure out, like for example, what is the
17 signature that should be observed when there's a modification of
18 cytosine. Is that fairly accurate? So if I'm --

19 MR. WISE: Well, what I'm struggling with is why you
20 would have all the same sequence.

21 JUDGE FITZPATRICK: I don't know. That's -- that
22 was, I thought, your position. I thought that's what you were
23 saying. In order to train the model, Flusberg uses sequence
24 identity that's constant, so it's just all, for example, cytosine. I
25 thought that's what --

1 MR. WISE: Well, no, the sequences are different, but
2 they're training them all using identical sequences. So you -- first
3 step, line up the sequences so I can eliminate nucleotide identity
4 from the equation, and I look at just the positions and I look at the
5 IPD ratios at the positions. And then when I see that one position
6 has, you know, got a huge spike or something, then I can go back
7 and look at the sequence and see if that's -- and call that as a
8 modification.

9 JUDGE FITZPATRICK: Okay, so -- yeah. So it's not --
10 I think earlier, I said -- I was imaging like 100 cytosines in a row
11 and then 100 cytosines that are unmodified. In fact, it sounds like
12 maybe it's a strand -- whatever it is, it's got all four bases,
13 presumably, if it's 100 times long. And then you're -- but they're
14 all unmodified, and then you're going to run through the identical
15 sequence strand. That is the same base line up, except one or more
16 of them may be methylated. Is that how it's done in Flusberg, in
17 your view?

18 MR. WISE: Well, I think we're now talking about the
19 White Paper or kineticsTools. So Flusberg, you know, as Counsel
20 pointed out is just a -- it's an observational kind of concept paper.
21 And so it doesn't, you know -- all it does -- it takes known
22 sequences and compares them. And the way it evolves is then it
23 can -- you have the data, you know, you have a model that lets you
24 compare the IPD ratios provided that you use identical sequences
25 to each other. That's what kineticsTools does. That's what the

1 White Paper does. They're looking at identical sequences and
2 comparing IPD ratios. That's it. That's as far as the art progressed
3 before the Lo method came out that you put nucleotide identity,
4 you put the position relative to your target, and you put all this data
5 in that allows you to have, you know, the equivalent of bisulfite
6 sequencing data that's been praised throughout the art and copied
7 by PacBio.

8 But as far as this technology got and, you know, even,
9 you know, Dr. Dessimoz agreed that with all these tools, you still
10 have to parse the data. It's not -- you still have to create the data
11 infrastructure no matter what it is. The BAM file is not the data
12 structure that allows you to practice the claim. Do you have any
13 more questions? Because I've got six minutes left.

14 JUDGE FITZPATRICK: I had a lot. I would like to
15 hear -- when I read the papers, I looked at your response to nexus,
16 the lack of nexus that Petitioner argued, for your secondary
17 considerations evidence. I read your response, I saw you had some
18 case law in it. You know, perfect, co-extensiveness is not
19 required. But then I -- that's all I saw. Is that your whole position?

20 MR. WISE: Well, I'm not quite sure what you mean on
21 the nexus, but let me go to the nexus. Hang on one second.

22 JUDGE FITZPATRICK: Okay.

23 MR. WISE: I'll give you my position on nexus. All
24 right. So first, what I want to say about nexus is, you know, we
25 provided evidence of unexpected results, long felt need, all of our

1 secondary considerations. Dr. Dessimoz testified that an
2 obviousness consideration requires a consideration of these
3 considerations. He couldn't recall considering any and he testified
4 he didn't look at any of the references that Dr. Koo had included
5 that were not in his declaration. And so while they criticized Dr.
6 Koo for not looking at every piece of evidence in the petition, Dr.
7 Dessimoz did not look at anything in our record at all.

8 So the nexus can be shown in two ways. We say it's the
9 invention that is disclosed and claimed and both experts agree it is.
10 So Dr. Dessimoz said, Exhibit 30, the Tse reference is the paper
11 that corresponds to the patent and he believes that Claim 1, the
12 model, the holistic kinetic model of Tse is Claim 1 of the patent.
13 And that's what Dr. Koo testified to, as well. So that, you know,
14 so --

15 JUDGE FITZPATRICK: I don't -- I just -- I'll just stop
16 you there. I'm not going to defer to that kind of testimony. There's
17 no way he knows the standard on nexus. So it's not just that Claim
18 1 covers what Tse did. It's whether what Tse did or describes is
19 also co-extensive with Claim 1, which essentially means there's
20 not a whole bunch of extra stuff that's possible. And here, we have
21 Claim 1 -- the way I understand it, Claim 1 leads on what Tse did
22 because Tse used a particular modification, 5mC, and that is one of
23 only many modifications that Claim 1 covers. And so factually --
24 I'm looking for your factual argument, if there is one, that that's not
25 accurate. Like is it -- does Tse -- do you have a position that Tse

1 describes other modifications than 5mC?

2 MR. WISE: I'd, you know -- I'd have to go back and
3 look at Tse, but the focus is 5mC and the reason it's focused on
4 5mC is that's the holy grail, if you will, in terms of protection
5 because that's what matters in million genomes in human. That's
6 what you detect for cancer and all of the things that are important.
7 And if you look at all of the praise that came as a result, you know,
8 in here, this nexus goes directly to the unique characteristics of
9 Claim 1, paragraph -- Slide 42 of Dr. Koo, paragraph 39, where he
10 describes the nexus between the features of the claim and how the
11 inventors probed for those features and decided what the optimal
12 claim set was that allowed you to have all the advantages that are
13 shown in the secondary considerations, and it's even praised by
14 others.

15 I mean, you've got others that are saying here on Slide --
16 the Birknerova Paper that identifies -- sorry, right here. They
17 start with -- the first sentence, they're talking about Flusberg, you
18 know, and then they tell you how great is Tse is relative to
19 Flusberg, which is the model, which is the input data structure and
20 how it gives you 99 percent correlation with bisulfate sequencing.
21 So bisulfate sequencing was a problem, it wasn't fixed. Their own
22 publications show that. The publications from others show that
23 bisulfate sequencing was not fixed. You couldn't do direct
24 detection of 5-Methylcytosine with SMRT sequencing until the Lo
25 method came out. This is Slide 58, the Birknerova Paper.

1 Completely unconnected to Lo, completely unconnected to
2 PacBio. They're just praising the invention. They're showing this
3 as an unexpected result because it has such a high correlation to
4 bisulfate sequencing and it solves the long felt need.

5 And, you know, if you look at it, at the end of the day,
6 what happens is they get an access to our paper and here's their
7 employee, Wenger, on Slide 63, saying, the technical ability to
8 interrogate these types of methylations from SMRT sequencing
9 was to demonstrate it in the Tse Paper and we've now integrated it
10 into the PacBio system. They copied it. And Dr. Koo gives you
11 the nexus. He tells you that you have to probe all the features,
12 figure out what the optimal feature set is, and he gives you that
13 nexus, and that's unrebutted. Dr. Dessimoz didn't come in and
14 testify and say, hey, you know, Lo -- you know, Koo is wrong on
15 this. That's unrebutted testimony from an expert in the field. And
16 with that, I might -- what do I got for time left?

17 JUDGE FITZPATRICK: I have you down for five more
18 minutes. For rebuttal, if you want to leave it for that.

19 MR. WISE: Sure. Unless you have other questions, I'll
20 leave it there.

21 JUDGE FITZPATRICK: No. So, we'll turn it back
22 over. Well, I'm sorry, Mr. Rosato. You're waiting for the -- you
23 can go ahead.

24 MR. ROSATO: Thank you. Patent Owner's slides are
25 still up on the share, which is fine by me. Just letting him know.

1 Thank you. Okay. So I mean, I'll identify a couple points and
2 answer any questions. One of -- you know, a slightly new
3 argument I heard was about the target position in the window, so I
4 just wanted to address that briefly and call attention to the --
5 Counsel's District Court infringement complaint, those were
6 submitted as Exhibit 1014, so at page 30 -- marked page 30 --
7 again, this is consistent with what we discussed earlier. At District
8 Court -- they're pointing to this exact same content from the BAM
9 file and there are infringement contentions and we see that there.
10 And I don't want to put it up on the screen because it's marked
11 outside Counsel's eyes only. There's no -- I'm not a District Court
12 counsel. I don't --

13 JUDGE FITZPATRICK: Understand. Appreciate that.
14 Would you give us that cite again, though?

15 MR. ROSATO: Yeah.

16 JUDGE FITZPATRICK: It was in Exhibit 1014?

17 MR. ROSATO: Exhibit 1014 and it's on page 30 where
18 they map specifically, element -- they label it 1B2. It's a position
19 of the nucleotide with respect to a target position within a window.
20 There's --

21 JUDGE FITZPATRICK: Okay.

22 MR. ROSATO: -- some commentary about the target
23 window, but they specifically point to the exact same image that
24 we see in the PacBio-BAM reference in this case, which is shown
25 on our demonstrative exhibit Slide 12, so that's exactly what

1 they're pointing to. So again, they're trying to sort of back pedal
2 from what they argued at District Court, but it's there. And
3 ultimately, this doesn't address the obviousness case that's brought.
4 I mean, there's a lot of argument that attacks, you know, not only
5 individual references individually, but it's even worse than that.
6 They're pulling out one experiment from one, you know, from one
7 reference and attacking that, like that's the whole body of prior art,
8 which it obviously isn't.

9 So again, there's an obviousness argument here. Their
10 rebuttal argument of this target position is not consistent with what
11 they argued. It's also not consistent with the -- you know, the
12 broader teachings of the art of record. This target position
13 concept, again, is -- all of the art is identifying a nucleotide of
14 interest and talking about a window around it, so that can't be
15 ignored. That -- we see that in the Flusberg Paper, again, shown
16 on Slide 9. It's specifically identifying position number 73 and
17 identifying the window around that. We see that in the Flusberg
18 patent.

19 In their formula, they're specifically identifying the target
20 nucleotide and then talking about context. That's illustrated in
21 Demonstrative Exhibit 11. Another example is the Clark
22 reference. I mean, it goes on and on and on, but just to give a few
23 examples, it -- our demonstrative exhibit, Slide 29, illustrates an
24 image from Clark, which is specifically identifying a target
25 position as -- I think he calls it position zero, identifies it by

1 nucleotide identity, and then also has the window over the stretch
2 of DNA that's being analyzed.

3 If you turn to Slide -- our demonstrative exhibit, Slide
4 27, this has one thing I wanted to point out. There are a lot of --
5 we see this in the briefing and I heard a lot more of it today, but
6 there are a lot of comments about, you know, what Dr. Dessimoz
7 said and he agreed with us. Dr. Dessimoz -- let's be perfectly
8 clear. Dr. Dessimoz has never agreed with anything they're
9 arguing here and there's nothing they point to that supports that.
10 Most of the time when they're pointing to their deposition
11 transcript, they're pointing to the lawyer's own questioning about
12 Dr. Dessimoz, not necessarily something that he said.

13 And this is most -- this is illustrated with this arguing
14 about holding constant or using as a variable. They keep saying
15 Dr. Dessimoz somehow agreed with that. He did not agree with
16 that. He disagreed with -- he expressly disagreed with them and
17 rejected this notion of some sort of bifurcation of constant versus
18 variable. Even in the very same part of the transcript that they
19 tend -- they kept pointing to saying, ah-ha, you agreed with us, he
20 goes on to specifically reject this dichotomy of fixed versus
21 variable, and then explains to them that the art -- his take was art
22 keeps telling us that it's important to take into consideration the
23 nucleotide -- the sequence information. And he's not going to
24 ignore that and therefore, it would not be ignored as they argued.
25 It'd be taken into consideration because it's precisely what the prior

1 art is instructing to do.

2 So Dr. Dessimoz has never agreed with them. Again,
3 that testimony is shown here on Slide 27. There's additional
4 testimony in his transcript, Exhibit 2037. Basically, spanning
5 pages 91 through 93, he rejects this whole argument again. So this
6 notion that he somehow agreed with them is just not accurate.

7 The final thing I would -- I don't believe this is lost on
8 the Board, but just to be clear, they keep pointing to this one proof
9 of concept experiment in the Flusberg paper with a comparison of
10 two sequences to show they can distinguish a methyl A
11 modification based on kinetic features. Again, this is one example
12 in one prior art reference, and they keep referring to that is
13 Flusberg generally. That does not address the full scope of
14 teachings of the Flusberg references and it certainly does not
15 address the full scope of prior art teachings. The Flusberg patent,
16 again, is talking about various different types of models, including
17 neural networks which they -- you know, which is what they're
18 pointing to in the Tse reference.

19 In terms of this notion, I want to turn back to Slide 11,
20 and consistent with that point, again, that there's this sort of
21 blinkered approach to looking at the prior art where they -- they're
22 sort of mischaracterizing what's there and ignoring what doesn't
23 help their argument. They point to the Flusberg patent as allegedly
24 excluding nucleotide identity and they're pointing specifically to
25 this provision of the Flusberg patent that's shown here in Slide 11

1 in the upper left box, but they cut it off right at the formula there.
2 The very next sentence states, in this example, a local context
3 extending three pulses to the left and three pulses to the right of
4 interest. And it's this type of, you know -- this is consistent with --

5 JUDGE FITZPATRICK: Sir, you have one minute.

6 MR. ROSATO: Thank you. This is consistent with
7 repeated commentary in the prior art emphasizing importance of
8 sequence information surrounding the base of interest, as well as
9 identification of this target position. Those are a few of the points
10 I wanted to make. I'm happy to answer any questions. I don't
11 think any of these arguments are at all consistent with the record
12 evidence or the prior art literature at the time. I don't think there's
13 a nexus. There clearly isn't and that's a big problem, but happy to
14 answer any further questions.

15 JUDGE FITZPATRICK: Nothing, but I'll -- just for both
16 parties, I just noticed in the beginning, you know, we all affirmed
17 that there was no protective order or sealed document, so if this is
18 something you have to clean up later on by filing a motion or
19 something, this Exhibit 10 -- was it 1014?

20 MR. ROSATO: Yes, 1014.

21 JUDGE FITZPATRICK: Yeah. You know, just follow
22 up if you need to, okay?

23 MR. ROSATO: Thank you.

24 MR. WISE: Michael Wise, again, Your Honor. So with
25 respect to 1014, in the briefing, we make it real clear that we do

1 not rely on the BAM file for element B, but rather, you create the
2 input data structure from the values that come from that BAM file,
3 and that's clear in the infringement contentions in the briefing.
4 Now, I'd like to look at Slide 18 -- our Slide 18. Can you put that
5 up, Mr. Hamilton?

6 Now, we just heard a lot about how we misquote Dr.
7 Dessimoz and he doesn't agree on the dichotomy. I asked him
8 right here on Slide 18, "Would you agree that this is fixed just like
9 the White Paper," and he says, "Well, as the name indicates, it is
10 controlled for in this case and yes, I think it's consistent with the
11 method that's described in the White Paper and the Flusberg
12 publications." He agrees that kineticsTools, the White Paper, and
13 the Flusberg publications, all the things that they rely on for their
14 premise that you would, you know, use it and input data structure,
15 that you do not use it as a variable in the input data structure
16 because it's fixed, because it's constant. The nucleotide identities
17 are the same. He agrees with that.

18 And then if we could go to Slide 27, the reason that you
19 do not -- the reason that using nucleotide identity in an input data
20 structure as a variable, as opposed to a constant as in Flusberg, is
21 not obvious is because they're not interchangeable. You can't
22 interchange them. It's right there. This is what he said. I asked
23 him. We were talking earlier about the two ways of doing it. One
24 is Flusberg method, which he says is holding a constant, and the
25 '794 method where you include all of these different variables.

1 Would a person in the art consider the two methods of taking into
2 account sequence context interchangeable? No.

3 They cannot be viewed interchangeably and the reason
4 they're -- and that's one of the reasons they -- it's not obvious and
5 the BAM file doesn't help you because it doesn't teach you to
6 modify the Flusberg method to take into account nucleotide
7 identity and position, along with interpulse duration and pulse
8 width. He agrees they're not interchangeable. Dr. Koo says
9 they're not interchangeable.

10 If you look at the next slide, Slide 28, he says you don't
11 get comparable data. Right here, he volunteers it. "Are you asking
12 me if the results -- if they might get the same data? Well, then no,
13 there'd be differences between the data." And at best, if we could
14 go to unexpected results, he says, I think they would be the same.
15 Right here. The Flusberg method I think would work -- you know,
16 Lo method -- my question, with Flusberg publications on hand and
17 the Lo methodology is in hand, what would a person in the art
18 expect? Instead of fixing sequence context, i.e., holding it constant
19 as you referred to it, we use the input structure of Lo. What would
20 you have thought in 2019? You'd get the same results, and you
21 don't.

22 Look at the next slide. Here in 2019, the inventors ran
23 the Flusberg experiment, you know, where they use pulse width
24 and interpulse duration, example 3 from the Flusberg Paper, and
25 compare it to their method and it's demonstratively better, and the

1 prior art recognizes them as better. That was the Birknerova
2 Paper. I'm on Slide 46, by the way, that we were talking about
3 before where they say, this data is just as good as bisulfate
4 sequencing. That was a long felt need that was solved by the Lo
5 inventors. And I want to go back to Claim 1, one more time.

6 JUDGE FITZPATRICK: Hang on one second, please.
7 This figure that is shown --

8 MR. WISE: Yep.

9 JUDGE FITZPATRICK: -- or that was shown, if you
10 could -- yeah, there it is. The red line is -- so like one would be a
11 perfect prediction, or --

12 MR. WISE: Yeah.

13 JUDGE FITZPATRICK: -- sequencing?

14 MR. WISE: Right.

15 JUDGE FITZPATRICK: And your -- this is -- I am
16 assuming red is what you're saying is your embodiment and it's --
17 yeah.

18 MR. WISE: It's also right there in the Koo declaration,
19 and then also --

20 JUDGE FITZPATRICK: Understood. Yeah, yeah. It's
21 more the --

22 MR. WISE: Yeah.

23 JUDGE FITZPATRICK: -- what is blue? How do I
24 interpret blue? I know that --

25 MR. WISE: Blue is --

1 JUDGE FITZPATRICK: -- you said -- yeah, go ahead.

2 Sorry.

3 MR. WISE: Blue is the Flusberg method. It says so
4 right in the figure ledger for 29. It shows the AUC for the two
5 principal components used in Flusberg's study, involving IPD and
6 PW. Much less accurate --

7 JUDGE FITZPATRICK: So they use both? So Flusberg
8 used pulse width, at least in this example?

9 MR. WISE: Yes. Oh, yes. As I said before, Flusberg --
10 Clark used pulse width and then after the White Paper and
11 kineticsTools in Schadt, PacBio stops using pulse width in the art.
12 They say you only use IPD only. That's what the teachings are.

13 JUDGE FITZPATRICK: All right. And then I have
14 another question and then you're pretty much out of your time, but
15 I want to ask this question.

16 MR. WISE: Yeah.

17 JUDGE FITZPATRICK: In step A, Claim 1, step A,
18 it's -- you can see that --

19 MR. WISE: Your Honor, can we pull that up real quick?

20 JUDGE FITZPATRICK: Sure. Yeah. I'm looking at the
21 version of mine, but that would help for everybody else. You're
22 saying that the PacBio-BAM file --

23 MR. WISE: Yeah.

24 JUDGE FITZPATRICK: -- is data -- that if you receive
25 that file, you are implementing step A. So you received --

1 MR. WISE: Yeah.

2 JUDGE FITZPATRICK: -- data that's described in step
3 A.

4 MR. WISE: That's right.

5 JUDGE FITZPATRICK: Now, if that data includes an
6 entity of the nucleotide and the position of the nucleotide within
7 the sample nucleic acid molecule, if that data is there, where's the
8 disconnect? How can you not create an input data structure that
9 would have features corresponding to that?

10 MR. WISE: You can and -- you can, but the question is
11 what do you do with the data and what's the teachings in the art.
12 And the Flusberg teachings of the art is to hold the nucleotide
13 constant. And the difference here is Lo is making the nucleotide
14 identity a variable by making it one of the -- by putting in the
15 identity for each nucleotide. In step B, the identity nucleotide, the
16 position the nucleotide relative to the target -- that's all the way as
17 a variable in the data matrix that gets fed -- that goes into the
18 model. And that -- don't forget, it's not any use of nucleonic tide
19 identity that matters.

20 It's a particular use that's used here to do the modification
21 detection and you have to train it with the exact same data sets.
22 The exact same input data properties. The exact same window, the
23 exact same sequence length and you do it thousands of times to be
24 able to train the model, and then when you do the modification
25 detection, you've got to use the same input structure. And the

1 Flusberg methods and all of the art that they're talking about, all of
2 the art that they've identified that's the premise of Ground 1,
3 basically makes nucleotide identity anonymous because they hold
4 it constant and they're just looking at positions relative to IPD or
5 PW ratios. You know, if you want to look before 2012. So --

6 JUDGE FITZPATRICK: Thank you.

7 MR. WISE: -- because the Flusberg limits us to -- I'm
8 sorry. Do you want me to stop, Your Honor?

9 JUDGE FITZPATRICK: Yeah, I -- we're pretty much
10 out of time. I'll give you one minute to -- without interrupting you
11 with questions -- to wrap up.

12 MR. WISE: I just wanted to give a quick summary,
13 Your Honor, and what I would say is this, is that all the art that
14 addressed detecting base modification using SMRT sequencing
15 shared one common teaching. Avoid using nucleotide identity as a
16 property and input data structure for detecting base modification
17 by keeping it constant. And then for six years after Schadt, the art
18 taught to not use -- to use IPD without pulse width. Petitioner
19 provides no reason a person of skill in the art would modify these
20 teachings to use the claim combination of nucleotide identity,
21 nucleotide position relative to target, pulse width in IPD properties
22 in an input data structure, and all of the secondary considerations
23 are tied to Dr. Koo's testimony about the direct -- about the
24 probing of all the various features and why the unique
25 characteristics of Claim 1 give you all the benefits that are copied,

1 that were praised, that resulted in unexpected result, that solved the
2 long felt need of doing direct detection of base modification with
3 smart sequencing, and not using bisulfate sequencing, and the
4 failure of others to achieve that. Thank you.

5 JUDGE FITZPATRICK: Thank you both. The panel --
6 the Judges don't have any further questions, so we will adjourn this
7 and if Counsel for both says -- if you guys could stay on and just
8 answer any questions -- the Judges, you can see, have disappeared.
9 If you guys could stay on and answer any questions that the Court
10 Reporter has, usually, spelling of peoples' names. Thank you.
11 And then we'll be issuing a decision in due course over the next
12 few months. Thank you.

13 MR. ROSATO: Thank you, Your Honor.

14 (Whereupon, the above-entitled matter went off the
15 record at 2:40 p.m.)

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