

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENEOSCOPY, INC.,	)
	)
Petitioner,	)
	) Case No.
vs.	) IPR2024-00459
	)
EXACT SCIENCES	) U.S. Patent
CORPORATION,	) 11,634,781
	)
Patent Owner.	)

The deposition of VADIM BACKMAN, taken
before Richard Derrick Ehrlich, Registered Merit
Reporter, Certified Realtime Reporter, taken at Barnes
& Thornburg, One N Wacker Drive, Chicago, Illinois,
commencing on the 15th day of January, 2025, at
9:00 a.m.

A P P E A R A N C E S

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I N D E X

	Page
Exam by Brendan Jones	4
Exam by Anastasia Fernands	162

E X H I B I T S

	Page
Exhibit No. 2021 -	6
Declaration of Vadim Backman	
Exhibit No. 2022 -	6
Declaration of Vadim Backman	
Exhibit No. 2008 -	69
Imperiale paper	
Exhibit No. 1004 -	91
"Analysis of Promoter Methylation in Stool, a Novel Method for Detection of Colorectal Cancer"	
Exhibit No. 1005 -	119
"Performance, Characteristics, and Evaluation of an Automated, Developed, and Quantitative Immunochemical Fecal Occult Blood Screening Test"	
Exhibit No. 1006 -	142
"Improved Fecal DNA Test for Colorectal Cancer Screening"	
Exhibit No. 2048 -	155
Schroy paper cited in Itzkowitz	

VADIM BACKMAN, DEPONENT, SWORN

EXAMINATION

BY MR. JONES:

Q Good morning, Dr. Backman.

A Good morning.

Q Have you been deposed before?

A No.

Q So this is your first time?

A Correct.

Q Okay. So I'm sure you've had some instructions conveyed to you by your counsel, but just a few of the ground rules I'll ask you to follow in this.

So the first rule is just wait until a question is complete before answering so that we aren't speaking over each other. It makes it really hard for the court reporter if we are both talking at the same time. That will give your counsel a chance to object.

Do you understand that?

A Sure.

Q Okay. Second rule is that please answer everything orally rather than nodding your head or shaking your head. Again, it's hard for the

1 court reporter to record nonverbal responses.

2 Do you understand that?

3 A Sure. Yeah.

4 Q If I ask you a question that you don't
5 understand, please ask me to clarify; otherwise,
6 my understanding would be that you understood
7 the question.

8 A Makes sense.

9 Q And then, as I said, we'll take a break every
10 hour or so, or I'll do my best to take a break
11 every hour or so. If, for any reason, you need
12 to take a break before I take a break, then just
13 please let me know. The only caveat being that
14 if there's a question pending, I'll ask you to
15 answer that question before we take a break.

16 A Sure.

17 Q Is there any reason why you can't give complete
18 and truthful answers today?

19 A No.

20 Q And so you have in front of you two documents.
21 One document is one you brought in with you. Am
22 I right in my understanding that that document
23 is Exhibit 2022, which is the second declaration
24 that you submitted in this IPR?

1 A Correct. Yeah.

2 (Exhibit No. 2021 marked.)

3 (Exhibit No. 2022 marked.)

4 BY MR. JONES:

5 Q Is that a clean copy of your declaration?

6 A By "clean," you mean without mark?

7 Q Yes.

8 A Yeah. I think it's clean, yeah. I just looked
9 at it. I think it's clean, yeah.

10 Q So no notes, no highlighting?

11 A I don't see any, no.

12 Q And then the other document, which I put in
13 front of you is Exhibit 2001 in this IPR, which
14 is the first declaration you submitted in
15 support of the patent owner's preliminary
16 response.

17 Do you see that?

18 A That's correct. Yeah.

19 Q Have you served as a technical expert in any IPR
20 proceeding before this?

21 A No.

22 Q Have you served as an expert in any litigation
23 matter before this?

24 A No.

1 Q Have you served as an expert in any other kind
2 of legal dispute?

3 A Legal dispute, no.

4 Q Outside of your engagement as an expert in this
5 proceeding, do you have any other relationship
6 with Exact Sciences?

7 A No.

8 Q The declarations you submitted in this
9 proceeding, they concern U.S. Patent 11,634,781;
10 correct?

11 A Correct.

12 Q So if we call that the '781 patent today, you'll
13 understand what I'm saying?

14 A Yeah.

15 Q Do you understand that the '781 patent has been
16 asserted by Exact against Geneoscopy in district
17 court litigation?

18 A Yes.

19 Q You understand that; right?

20 A I do. I understand, yes.

21 Q Have you reviewed any documents filed in the
22 district court litigation?

23 A Could you clarify which documents you're
24 referring to?

1 Q Have you reviewed any declarations by technical
2 experts that were submitted in the district
3 court litigation?

4 A Well, I presume that declarations by Dr. Whitney
5 is part of that. I reviewed those, yes.

6 Q So I understand you reviewed Dr. Whitney's
7 declaration submitted in the IPR proceeding;
8 correct?

9 A Yes.

10 Q Do you know whether you've submitted -- reviewed
11 any other declarations submitted by Dr. Whitney?

12 A There were several, right. So one of them was
13 the IPR. The other one, I reviewed
14 Dr. Whitney's testimony as well, and I reviewed
15 Dr. Whitney's response to Dr. Patterson's
16 testimony.

17 Q So you reviewed Dr. Whitney's declaration in
18 response to Dr. Patterson's declaration?

19 A Correct. Yeah.

20 Q And that was the declaration that was submitted
21 in the district court litigation?

22 A Okay.

23 Q Did you review any declarations by
24 Dr. Patterson?

1 A No.

2 Q You mentioned you reviewed Dr. Whitney's
3 deposition testimony; right? Correct?

4 A Correct. Yeah.

5 Q Do you recall how many of Dr. Whitney's
6 depositions you've read transcripts of?

7 A How many -- I'm just familiar with one
8 deposition that he had a couple months ago.
9 Several months ago. I read the transcript.

10 Q You read the transcript.

11 Have you read any other deposition
12 transcripts besides the Dr. Whitney transcript
13 you just mentioned?

14 A I don't think so.

15 Q Have you ever met Dr. Patterson before?

16 A No.

17 Q Have you spoken with Dr. Patterson at all about
18 the subject matter of your declarations?

19 A No.

20 Q Were you aware that Exact used Dr. Mark Eschoo
21 as a technical expert in the district court
22 litigation?

23 A No.

24 Q So you haven't read any declarations by

1 Dr. Eschoo?

2 A I don't think so.

3 Q And you've never -- have you ever met Dr. Eschoo
4 before?

5 A No.

6 Q And you haven't read a deposition transcript of
7 Dr. Eschoo; right?

8 A No.

9 Q Do you recall when you were retained as an
10 expert for this IPR proceeding?

11 A That was early February 2024. That's when I
12 signed the contract.

13 Q Okay. How were you -- sorry. Scratch that.

14 Who contacted you about potentially serving
15 as an expert in this litigation, I mean, in this
16 IPR proceeding?

17 A So this was Cahn Litigation Services. I believe
18 it's a company specializing in retaining expert
19 witnesses, and that was back in 2023.

20 Q In 2023?

21 A Yes. November -- right after Thanksgiving.
22 November 28, I think.

23 Q That's a good memory.

24 A It was an eventful Thanksgiving. Not because of

1 that.

2 Q And someone from that initial contact with
3 someone from Cahn Litigation Services?

4 A I received an email from them.

5 Q What did they tell you in the email about the
6 potential matter?

7 A There were very, very few, if any, specifics.
8 They did say that they are looking for an expert
9 witness that is related to colonoscopy practice
10 and colon cancer screening, which is my
11 expertise. They did mention Exact Sciences.
12 There were no other details about, you know,
13 patents, any -- no numbers, no other disclosures
14 of subject matter.

15 Q So this is -- this email was sent in November of
16 2023; correct?

17 A Correct. Yeah. The end of November 2023.

18 Q Did you respond to the email in November of
19 2023?

20 A I did.

21 Q And did you have further communications with
22 anyone about the potential matter prior to
23 February of 2024?

24 A I did ask about -- I asked a few questions about

1 timeline. I did not ask about -- any questions
2 about the details of the case.

3 Q Who did you ask questions about timeline to?

4 A Cahn Litigation.

5 Q And when did these -- the communications, when
6 you asked questions about timeline, take place?

7 A December 2023.

8 Q Did you discuss anything else about the case in
9 your conversations about -- where you asked
10 about timeline with Cahn Litigation?

11 A You're asking if I asked any other questions
12 other than timeline?

13 Q I'm just asking if anything else was discussed
14 in those communications.

15 A There were a couple of other things, primarily
16 related to my expertise -- my experience, or
17 lack thereof, in litigation, consultations.
18 Primarily those kinds of questions.

19 Q Anything else that you recall?

20 A No.

21 Q And when did you next communicate with anyone
22 about the potential engagement?

23 A We had a couple of Zoom meetings with counsel
24 where I received a little more details about the

1 case.

2 Q And when did these meetings take place?

3 A January 2024.

4 Q In those meetings, what were you told about the
5 case?

6 A I was told about the Geneoscopy, their work and
7 potential infringement on the '781 patent. I
8 was told that they are arguing that the patent
9 was -- should be invalid. I don't recall a lot
10 of -- and we did talk about a few general things
11 related to, again, to my expertise, my prior
12 work.

13 I don't really remember a lot of other
14 aspects of what we talked about.

15 Q What were you told about Geneoscopy's work and
16 potential infringement?

17 MS. FERNANDS: I would just caution you to
18 limit before -- any conversation before you were
19 engaged.

20 MR. JONES: Right.

21 BY MR. JONES:

22 Q So prior to your engagement in February of 2024,
23 in the Zoom calls in January of 2024, what were
24 you told about Geneoscopy's work and potential

1 infringement?

2 A I don't recall that I was told a lot of
3 specifics; however, I had seen -- by that time,
4 I had seen a paper related to Geneoscopy's work
5 published in JAMA 2023. Again, that's part
6 of -- it's part of my expertise. It's part of
7 the research that I periodically do. So I was
8 familiar with that work scientifically. Their
9 work in combining NMA markers with it. And it
10 was a high-profile article. JAMA is a journal,
11 obviously.

12 So I was asked -- I remember I was asked
13 what I think about the work.

14 Again, we did not discuss details of which
15 aspects of '781 patent Geneoscopy thinks are
16 nonobvious. We don't get into any of the legal
17 details, details of the case. It was primarily
18 more of a scientific discussion than anything
19 else.

20 Q When you were asked what you thought about
21 Geneoscopy's work, what did you -- how did you
22 answer?

23 A By the way, the question did not deal with the
24 infringement, per se. It was -- like I said, it

1 was more of the what do I think about the work.

2 What do I think about the paper.

3 Q How did you answer when you were asked what you
4 thought about the work or the paper?

5 A I mentioned that there were positives and
6 negatives over the work from a scientific
7 perspective. It was a fairly large study. It
8 was over 8,000 patients, you know, clearly a
9 well-constructed study. There were positive
10 aspects, such as it was a multicenter study.
11 The mix of patients appeared to be quite
12 reasonable. So I discussed details of
13 the clinical work.

14 I do have -- we talked about sensitive and
15 specificity of the results. I did have
16 concerns, however, that looking at the data they
17 provided, the AUC, area under the
18 receiver/operator or ROC curve for FIT, and
19 their combined tests seemed to be quite similar.

20 So from the scientific perspective, that
21 was a finding, when I -- I remember when I read
22 the paper, that alerted me. You know, I kind of
23 was asking myself whether -- how much
24 improvement this test actually have over FIT,

1 and this in their data.

2 Q So in the previous answer, you mentioned that in
3 January 2024, you had Zoom meetings with
4 counsel.

5 Do you recall how many Zoom meetings with
6 counsel you had in January 2024?

7 A I would not say with complete certainty, but I
8 think there were two.

9 Q Do you recall who was -- who attended those Zoom
10 meetings?

11 A I don't remember names.

12 Q Do you remember anyone who was on the Zoom call,
13 either Zoom call?

14 A I can't give names. I can't remember. I would
15 need to check my records.

16 Q Do you recall whether the people on the Zoom
17 meetings were attorneys with Quinn Emanuel?

18 A I think so.

19 Q Do you know if anyone on the Zoom meetings were
20 employees of Exact Sciences?

21 A No, I don't think so. I don't think any -- at
22 least I was not aware if anybody was there from
23 Exact Sciences. I was not told that.

24 Q Do you recall the approximate length of the

1 first Zoom meeting?

2 A It was close to 45 minutes.

3 Q And do you recall the approximate length of the
4 second Zoom meeting?

5 A About the same.

6 Q Did you discuss the '781 patent in either of
7 those meetings?

8 A By the time of the meetings, I was sent a copy
9 of the '781 patent, which I was not necessarily
10 asked to review, but I volunteered and looked
11 over it myself. So I was -- by that time, I was
12 familiar with it, with the patent.

13 Q In either of the January 2024 meetings, did you
14 discuss any aspect of the '781 patent?

15 A I don't think so. What I did, however, say --
16 volunteered information that, from my
17 perspective, the most critical aspect of the
18 patent is the combination of FIT and nucleic
19 acid markers. And from my perspective, that
20 was, indeed, a significant innovation. I
21 remember I volunteered this information.

22 Q Why did you consider the combination of FIT and
23 nucleic acid markers a significant innovation at
24 that time?

1 A For a variety of reasons. As you probably know,
2 you know, I've been active in colon cancer
3 screening research since -- well, even before
4 2001, when I started my appointment at
5 Northwestern.

6 So the time from 2001 to 2009, which is the
7 year of filing the patent, was the beginning of
8 my independent research career.

9 So I was part of the, you know, part of the
10 research committee. I was very active at the
11 time, of course, and trying to do as much as I
12 could, trying to learn as much as I could. And
13 this was -- I served on the Early Detection
14 Research Network Steering Committee and National
15 Cancer Institute Body responsible for
16 biomarkers. So I was kind of in the midst of
17 everything that was going on.

18 And, you know, I remember the time that
19 everybody wanted to find a way to screen for
20 colon cancer. That was an important thing. And
21 nobody, at the time, was thinking of combining
22 fecal occult blood test with molecular markers,
23 especially nucleic acids biomarkers.

24 Gene mutations were the predominant view of

1 the field. That's where cancer is. That is the
2 genealogy of cancer. That's what people wanted
3 to focus on, you know, in publications, in
4 grants, in clinical trials that NCI was
5 considering funding.

6 So I remember the time. I remember the
7 time. And it was actually somewhat of a
8 surprise to a lot to people. It went against
9 the grain of the prevailing opinion at the time
10 when Exact Sciences made the decision to combine
11 fecal occult blood test with the nucleic acid
12 biomarkers. So I remember the time.

13 And, frankly, back in the day, I was not
14 really concerned about patents prior to 2009,
15 let's say. But when I saw the patent, I
16 immediately recognized, when I saw, you know,
17 the basic claims, the first few independent
18 claims, I immediately recognized that. That
19 actually -- that is a significant innovation
20 because it came as a significant surprise to
21 everybody -- most people at the time -- that
22 these two things can be combined, and they can
23 be beneficial. Like I said, it went against the
24 prevailing opinion of most experts.

1 Even back -- you know, back in the day, I
2 felt this was a significant innovation. And
3 when I saw the patent, I kind of put two and two
4 together. And that is why I volunteered that
5 opinion.

6 Q Do you know who filed the priority application
7 in 2009 for the --

8 A I may not be able to pronounce the name
9 correctly. Do we have a -- the last name starts
10 with an "L."

11 Q Joost Louwagie?

12 A Okay. I will take that.

13 Q I asked Dutch friends how to pronounce his name.

14 A Okay. Good. Thank you. I need to practice
15 that a few times.

16 Q Do you know who Dr. -- who employed Dr. Louwagie
17 in 2009?

18 A I don't. I don't know.

19 Q Do you understand that he was employed by a
20 company called OncoMethylome?

21 A Now that you told me.

22 Q You didn't work with --

23 A I was not aware of it, no.

24 Q Do you know whether Joost Louwagie was ever

1 employed by Exact Sciences?

2 A I don't know.

3 Q Do you know when Exact Sciences first acquired
4 ownership of the '781 patent, or the family that
5 gave rise to the '781 patent?

6 A I don't know.

7 Q So you don't recall that the family that gave
8 rise to the '781 patent was first hired by Exact
9 Sciences in 2017?

10 A No, I did not know that. I know it was filed in
11 February of 2009.

12 Q And you aren't aware that it was filed in
13 February of 2009 on behalf of a company called
14 OncoMethylome?

15 A No, I don't think I knew that.

16 What I do know is that Exact Sciences --
17 you know, they had been working for quite some
18 time around the time on combination of FOBT and
19 nucleic acid markers. And they obviously, of
20 course, did a significant trial that was
21 published. Imperiale, the lead author, I
22 believe in 2014.

23 So you mentioned 2017 was the date of the
24 acquisition of the patent. I was not aware -- I

1 did not have this information, but it appears to
2 me that Exact Sciences, regarding of the date
3 of -- acquisition date, they had worked on
4 the -- on combining those biomarkers prior to
5 2017.

6 Q Okay. Taking a step back again. After the two
7 Zoom meetings with counsel in January of 2023 --

8 A January 2024.

9 Q Sorry. My mistake.

10 A I was first contacted by Cahn Litigation in
11 November 2023, but meetings with counsel were in
12 January 2024.

13 Q Yeah. That was my fault. I apologize.

14 So after the two Zoom meetings with counsel
15 in January 2024, did you have any further
16 meetings or discussions with anyone concerning
17 the subject matter of your declaration prior to
18 your engagement in February of 2024?

19 A I don't recall if I did.

20 Q When you say you were engaged, or you said you
21 were engaged, I believe, in early February of
22 2024?

23 A Yeah. If we count the date of engagement from
24 the day when I signed the engagement agreement,

1 yeah. That would be first week of
2 February 2024, I think.

3 Q Okay. So jumping ahead to your preparation for
4 this deposition today. Without revealing the
5 substance of any conversations with counsel,
6 what generally did you do to prepare for this
7 deposition?

8 A Well, we did have several meetings with counsel.
9 The preparation primarily concerned going over
10 legal standards.

11 MS. FERNANDS: Don't reveal the substance
12 of the preparation.

13 BY MR. JONES:

14 Q Just meetings with counsel -- I'm going to just
15 head it off to make sure you understand, because
16 I understand it is your first deposition.

17 So you can just -- if you just say, like,
18 whether you had meetings or not, and then we can
19 ask whether you reviewed documents, things like
20 that. But don't -- so I'm going to ask the
21 question again, and then hopefully we can get a
22 clean answer where you don't inadvertently
23 reveal privilege.

24 What did you do to prepare for this

1 deposition today? Or what did you do to prepare
2 for this deposition?

3 A We had a few meetings with counsel.

4 Q How many meetings did you have with counsel?

5 A We had a couple of Zoom meetings, and then two
6 meetings this week in person.

7 Q So when did the first of the Zoom meetings take
8 place?

9 A It was a couple weeks ago.

10 Q When you say "a couple," you mean about two
11 weeks ago?

12 A Well, actually, two weeks plus. A couple weeks
13 plus. It was the end of 2024. So
14 December 2024, right before the holidays.

15 Q About how long was the first of those meetings?

16 A They were about one hour. I think one of them
17 was pretty much one hour. The other one was an
18 hour and a half.

19 Q So the one-hour meeting was the end of
20 December 2024; right?

21 A Both of them were the end of December.

22 Q Do you recall who was on the first of those Zoom
23 calls?

24 A Both times were just counsel and me.

1 Q Okay. Was it Anastasia?

2 A Anastasia.

3 Q Anyone else?

4 A No. Just the two of us.

5 Q Then I believe you said you had two meetings in
6 person this week?

7 A Correct. Yeah.

8 Q When was the first of these meetings?

9 A On Monday.

10 Q How long was that meeting?

11 A Two hours, 45 minutes.

12 Q Two hours and 45 minutes?

13 A Almost three hours, yeah.

14 Q And who was present at that meeting?

15 A Just the two of us.

16 Q And when you say "just the two of us," you mean
17 you and Anastasia?

18 A Anastasia, yes.

19 Q And then when was your second meeting?

20 A Yesterday.

21 Q And about how long was that meeting yesterday?

22 A I believe we started at 9:30 and ended about --
23 close to 5:00. So a couple of breaks. Seven
24 hours.

1 Q Was it just you and Anastasia at that meeting as
2 well?

3 A That's correct.

4 Q Did you review any documents in preparation for
5 this deposition?

6 MS. FERNANDS: Caution. That's a yes-or-no
7 question.

8 THE DEPONENT: Huh?

9 Yes, I did.

10 BY MR. JONES:

11 Q Did you review any documents other than those
12 that were cited in your declarations?

13 A I don't think so.

14 Q Okay. If you could look at -- there's a
15 declaration in front of you, which is Exhibit
16 2001, which is the first declaration you
17 submitted in this IPR proceeding.

18 Do you see that?

19 A Yeah.

20 Q And you recognize this document as being, in
21 fact, the declaration -- the first declaration
22 you submitted in this IPR proceeding; right?

23 A I think so.

24 Q And if you go to page 42 of the declaration.

1 Is that your signature on page 42?

2 A Correct. Yes.

3 Q Did you write this declaration?

4 A I did. Some of the edits were done by counsel;
5 but other than that, yes, it is my work.

6 Q So you drafted this with some assistance of
7 counsel?

8 A Correct.

9 Q Did you read this declaration carefully before
10 signing it?

11 A I did.

12 Q Do you recall how much time, about, you spent
13 preparing your first declaration here?

14 A I may have to go back through my records to give
15 you an exact number. I do have it recorded. I
16 would say probably 50 hours.

17 Q Okay. Turning your attention to Exhibit 2022,
18 which is your other declaration.

19 Do you recognize this document as the
20 second declaration you submitted in this IPR
21 proceeding?

22 A I do.

23 Q Once again, can you turn to page 80 of this one?

24 Is that your signature on this declaration?

1 A Correct. Yeah.

2 Q Did you write this declaration with assistance
3 of counsel as well?

4 A Correct. Yes.

5 Q And did you read this declaration carefully
6 before signing it?

7 A I did.

8 Q Do you recall approximately how much time you
9 spent preparing your second declaration?

10 A So some of the materials in data analysis that
11 was in the second declaration was also borrowed
12 or modified, edited from the first.

13 So if you count all the work combined that
14 eventually ended up in the second declaration,
15 that would be over 100 hours.

16 Q The over 100 hours accounts for the time you
17 spent cumulatively preparing both declarations?

18 A Right. So 100 hours would be the time I spent
19 on the information, or writing that eventually
20 ended up in the second declaration.

21 Q So let me just ask that a different way.

22 So the total time you spent preparing both
23 of these declarations cumulatively would be --

24 A Over 100 hours.

1 Q -- over 100 hours?

2 A Yes.

3 Q Let me just remind you to wait until the
4 question is answered so that -- just to make
5 sure it's clear.

6 The time you spent preparing both of these
7 declarations cumulatively would be over 100
8 hours?

9 A That is correct.

10 Q Do you recall about how much over 100 hours?

11 A 130. Something along those lines.

12 Q If you look at your second declaration, and you
13 turn to paragraph 11 of the declaration.

14 A I see it, yes.

15 Q So you'll see in paragraph 11, you list
16 materials you reviewed in advance of preparing
17 this declaration.

18 Do you see that?

19 A I see that.

20 Q Besides what is listed in paragraph 11, are
21 there any additional documents you considered
22 while preparing your second declaration that are
23 not listed here?

24 A I don't see references and older literature that

1 went into -- prior art literature that went into
2 the declaration listed here in this paragraph.
3 And so I think it would be what's in this
4 paragraph plus all those references.

5 Q So if you look at the first sentence of the
6 paragraph, you mention you reviewed the petition
7 for inter partes review, the exhibits thereto,
8 including the '781 itself, the declaration of
9 Duncan Whitney, and the references cited in the
10 petition?

11 A Oh, yes. References cited in the petition, yes.

12 Q To the best of your knowledge, those would be
13 the references you referred to as far as prior
14 art references?

15 A Correct. Yes. There were several references
16 that were not included that I reviewed. They
17 were not included and were cited in this work
18 because they were not found to be either --
19 relevant, but I did do extensive literature
20 search.

21 Q So in the paragraph on page 6, so the second
22 half of the paragraph, you mention that you are
23 aware that Exact Sciences had filed a
24 continuation application. You cite family

1 application number 18,919,170.

2 Do you see that?

3 A Yeah, I see that.

4 Q Did you review that application prior to
5 submitting your declaration?

6 A No. I'm aware that it was filed. I did not
7 review.

8 Q And then on the previous page, you say you are
9 also aware that Geneoscopy has filed a petition
10 for inter partes review of Exact Sciences' U.S.
11 Patent Number 11,970,746, the '746 patent.

12 Do you see that?

13 A Correct. Yes.

14 Q You reviewed the '746 patent prior to preparing
15 this declaration; right?

16 A I did.

17 Q Other than the '746 patent and the '781 patent,
18 are there any patents and applications in the
19 '781 patent's family that you also reviewed?

20 A I don't think so.

21 Q Since submitting this declaration, have you --
22 I'm just going to clarify my last question by
23 timeframe.

24 Since submitting this last declaration,

1 have you reviewed any patents or applications in
2 the '781 patent family, other than the '746
3 patent and the '781 patent?

4 A I don't think so.

5 Q So in the very last sentence of this paragraph,
6 you say, "I will consider Joost Louwagie's
7 petition for review concerning the '746 patent
8 and the Exact Science ongoing patent prosecution
9 for the same patent family to the extent that
10 such information becomes relevant to my
11 opinions."

12 A Uh-huh.

13 Q So have you considered any ongoing patent
14 prosecution in same patent family prior to
15 coming into this deposition?

16 A Well, these are the two -- these are the patents
17 that I'm familiar with. I can't really talk
18 about other patents that might potentially
19 belong to this family. I don't think I reviewed
20 them.

21 Q I think we have the answer to this question, but
22 just to be more specific. You mentioned here on
23 page 5 that you have reviewed the board's
24 institution decision and the transcript of the

1 October 10, 2024 deposition of
2 Dr. Duncan Whitney.

3 Do you see that?

4 A Yes.

5 Q So that's the deposition transcript of
6 Duncan Whitney you referred to earlier?

7 A Yes.

8 Q And just to be clear, you don't have any
9 recollection of reviewing any other deposition
10 transcripts of depositions of Dr. Whitney; is
11 that right?

12 A No, I don't think so.

13 Q So you don't recall reviewing a deposition
14 transcript from his October 11th, 2024
15 deposition in the district court litigation
16 matter?

17 A I reviewed one deposition.

18 Q Okay.

19 A And I think it was October 10th.

20 Q Okay. And, again, I think I know the answer,
21 but just to be explicit. You haven't reviewed a
22 deposition transcript from his January 9th
23 deposition in the district court litigation
24 matter?

1 A No.

2 Q Are you aware of a company called ASP Health?

3 A ASP Health?

4 Q Yes.

5 A Yes, I'm aware of it.

6 Q You co-founded ASP Health in 2019; right?

7 A The company was a spinoff of another company
8 that I did co-found. So I don't think I
9 technically qualify as a co-founder, and I'm not
10 a member of the board.

11 Q Do you have any affiliation with ASP Health?

12 A I'm one of the stakeholders, but I don't serve
13 on the board. I'm not one of the directors or
14 executives of the company.

15 Q Do you spend any time working on behalf of ASP
16 Health?

17 A I don't.

18 Q And what was the company that ASP Health was
19 spun off of?

20 A That was NanoCytomics. A company called
21 NanoCytomics, but ASP was formed as a new
22 company.

23 Q Stepping back to ASP Health. What's the --
24 extremely high level, what does ASP Health do?

1 A It's developing a device that could be -- that
2 can be used to better prepare psychological
3 samples in the procedure called ROSE, R-O-S-E.
4 It's a rapid onsite psychological examination
5 procedure. For example, when final aspiration
6 is taken, for example, breast cancer detection,
7 there is a need to prepare a sample quickly and
8 in a way that it can be analyzed by a cytologist
9 right onsite during the procedure as opposed to
10 send the sample for analysis that could be done,
11 you know, days, weeks later, to prevent the need
12 to bring patient back for repeat procedure. And
13 that is the technology that ASP is developing,
14 how to deposit cells in a way that it can be
15 done quickly, and it can be processed and
16 analyzed right onsite.

17 I hope it's clear.

18 Q That is a more than sufficient response.

19 A Thank you.

20 Q To the best of your knowledge, does ASP Health
21 have any relationship with Exact Sciences?

22 A I'm not aware of any, and I can't really think
23 of any reason why they would.

24 Q So you mentioned that ASP Health was spun off of

1 or some other way originated from a company
2 called NanoCytomics?

3 A Uh-huh.

4 Q And that's a company that you said you
5 co-founded?

6 A I did.

7 Q When did you co-found NanoCytomics?

8 A I can't remember the exact date. I believe that
9 was around year 2012.

10 Q To the best of your knowledge, what's the
11 current status of NanoCytomics? Is it still an
12 existing, functioning company?

13 A No. It's essentially a holding company. It was
14 founded as essentially a commercial research
15 lab, doing a few preliminary studies in the risk
16 and technology. It's a holding company
17 essentially. It's not functional right now.

18 Q Do you currently spend any time working on
19 behalf of NanoCytomics?

20 A No. There's not much work to talk about.

21 Q Are you aware of a company called American
22 BioOptics?

23 A I do, yeah.

24 Q Do you have a relationship with American

1 BioOptics?

2 A The company is no longer functional. It was
3 founded -- I was one of the co-founders back in
4 2006, but the company is no longer functioning.

5 Q Going back to what's left of NanoCytomics.

6 A Uh-huh.

7 Q Are you aware of any relationship between
8 NanoCytomics and Exact Health?

9 A Exact Sciences?

10 Q Exact Sciences, yes.

11 A No.

12 Q Are you aware of any relationship that American
13 BioOptics had with Exact Sciences?

14 A No.

15 Q Do you currently do any work as a consultant of
16 Johnson & Johnson?

17 A No.

18 Q Have you previously done working as a consultant
19 of Johnson & Johnson?

20 A A very long time ago, when I was in grad school.
21 It was back in the '90s.

22 Q Do you currently serve as a consultant with
23 Morningside Evaluations and Consulting?

24 A Unh-unh.

1 Q Have you ever served as a consultant with them?

2 A There was a brief period of time. It was a long
3 time ago.

4 Q When you say "a long time ago," do you have -- a
5 decade?

6 A Probably more.

7 Q I meant what decade?

8 A How long time ago?

9 Q What decade did you work as a consultant for
10 Morningside Evaluations and Consulting, if you
11 recall?

12 A Right. Well, I can't recall exactly. I think
13 it was maybe 15, 20 years ago.

14 Q At an extremely high level, what was the subject
15 matter of that consulting work?

16 A Well, there were just recruiting consultants for
17 a variety of topics, and I was one of them they
18 contacted. I don't remember the subject of the
19 consultation, actually.

20 Q Okay. Do you serve as a consultant for Round
21 Table Group?

22 A I'm on the list of their consultants.

23 Q Have you done any work as a consultant for Round
24 Table Group?

1 A Periodically, they ask me if I want to consult
2 on some -- you know, talk to some of their
3 clients.

4 Q Is there a particular subject matter on which
5 you serve as a consultant with the Round Table
6 Group?

7 A Cancer therapeutics, one of them; epigenetic
8 drugs, cancer biomarkers.

9 Q About how much time in a given year would you
10 say you spend as a consultant for Round Table
11 Group?

12 A A few hours.

13 Q Did you currently serve as a consultant for
14 Guidepoint Global Advisors?

15 A Correct. It's a similar setup. They
16 periodically ask me if I want to consult with
17 some of their clients.

18 Q At a high level, what subject matter would that
19 consulting be on?

20 A It would be similar. Epigenetics -- epigenetic
21 drugs for cancer therapeutics, cancer
22 biomarkers.

23 Q In any of your consulting jobs, have you ever --
24 aside from this IPR proceeding, have you ever

1 done any consulting for Exact Sciences?

2 A No.

3 Q Have you ever done any consulting for
4 Geneoscopy?

5 A No.

6 Q Do you have experience processing human fecal
7 samples?

8 A I do.

9 Q When did you first do work processing human
10 fecal samples?

11 A I believe that was -- the actual work, I think,
12 started in 2006.

13 Q What was the nature of that work?

14 A We were interested in using fecal samples to
15 understand -- better understand progression of
16 colorectal carcinogenesis, and the role, what is
17 called field carcinogenesis.

18 Q Could you -- oh, did you say "fetal
19 carcinogenesis"?

20 A Field.

21 Q F-I-E-L-D?

22 A Correct. Yeah, as in field of study. Field of
23 carcinogenesis.

24 The preliminary work that led to that study

1 started earlier, of course, and that work
2 started around 2002, 2003. But the actual work
3 on fecal samples was 2006.

4 The idea was, like -- do you want more
5 details?

6 Q Yes, please.

7 A Okay. So the idea of the study was to collect
8 mucus level, mucus colonocytes from stool
9 samples, and investigate their biomarkers as a
10 function of progression of carcinogenesis at
11 different time points and correlate them with
12 other clinical findings. So that included a
13 sample of processing isolation, cell isolation,
14 and molecular analysis and the structural
15 analysis of cells.

16 Q What types of biomarkers were you analyzing from
17 those fecal samples?

18 A It was a fairly comprehensive panel starting
19 with the gene mutations, epigenetic alterations,
20 mRNA alterations, and chromatin alterations.

21 Q Did you look at any protein biomarkers in the
22 fecal samples?

23 A No. I presume you're talking about hemoglobin
24 proteins. Protein expression.

1 Q Did you look at whether or not any proteins
2 were -- any specific proteins were present in
3 the fecal samples you were analyzing?

4 A No.

5 Q Did you look at gene expression in the fecal
6 samples?

7 A Yes.

8 Q What was the source of the fecal samples that
9 you were analyzing in this 2006 timeframe?

10 A I'm sorry. Can you clarify what you mean by
11 "source"?

12 Q How did you acquire the fecal samples that you
13 were analyzing?

14 A We started with an animal study. So there were
15 fecal samples from animals. We have to pick
16 them up.

17 Q Did you analyze human fecal samples in that
18 study?

19 A No.

20 Q Do you have any experience analyzing human fecal
21 samples?

22 A I have experience analyzing the data from human
23 fecal samples. I did not process human fecal
24 samples with my hands in the lab.

1 Q So in what work did you analyze data from fecal
2 samples?

3 Sorry. Let me clarify my question because
4 that was more general.

5 When you refer to you have experience
6 analyzing data from human fecal samples, what
7 work are you referring to?

8 A Publicly available sequencing data, biomarker
9 data, again, from -- collected by other labs,
10 yeah.

11 Q What was the approximate time period in which
12 you were analyzing this data from human fecal
13 samples?

14 A Similar timeframe. Probably starting in 2007,
15 and, I mean, until now, we periodically, as part
16 of our research, analyze available data. The
17 most recent analysis was done last year, I
18 believe.

19 Q Do you have any experience developing buffers to
20 preserve analytes in fecal samples?

21 A We do not do experiments on developing -- we
22 don't develop any buffers. We use commercially
23 available buffers or their combination. We're
24 not a buffer lab.

1 MR. JONES: We've been going more than an
2 hour, so why don't we take a short break.

3 THE DEPONENT: Sure.

4 (Break.)

5 BY MR. JONES:

6 Q If you turn to page 12 of your declaration. And
7 then referring to your -- generally speaking,
8 I'm going to be referring to your second
9 declaration. It is Exhibit 2022.

10 A Okay.

11 Q So if you look at paragraph 30, and, actually,
12 on page 13, it goes over --

13 Do you want me to pause?

14 MS. FERNANDS: If you don't mind.

15 MR. JONES: Let's go off the record a
16 moment.

17 (Off the record.)

18 BY MR. JONES:

19 Q Okay. So we're in paragraph 30 of your second
20 declaration. And then the very last sentence of
21 the paragraph, you write, "Low sensitivity
22 results in disease not being detected, while low
23 specificity results in an unacceptable number of
24 false positives, which then lead to unnecessary

1 colonoscopies."

2 Do you see that?

3 A I do, yeah.

4 Q You'll agree with me that if colorectal cancer
5 is not detected, then the subject will go
6 untreated; right?

7 A Even if colorectal cancer does not get detected
8 by a combination of screening regimen, then
9 patient will get untreated until they develop
10 symptoms, which usually -- I agree with that,
11 yes.

12 And by "combination of screening regimen,"
13 I mean colonoscopy and any other tests that
14 might lead -- that might be appropriate prior to
15 colonoscopy.

16 Q If a patient with colorectal cancer goes
17 untreated, that could result in the patient's
18 death; right?

19 A It certainly can. There's a clear correlation
20 between the stage and diagnosis and five-year
21 mortality. Symptomatic patients have
22 significantly higher mortality and lower
23 five-year survival than those diagnosed at
24 earlier stages, for sure.

1 Q You'll agree with me that a high sensitivity for
2 detection of colorectal cancer is a desirable
3 feature in a diagnostic assay?

4 MS. FERNANDS: Objection. Form.

5 THE DEPONENT: Right. So you asked if
6 sensitivity is a desirable feature. It is
7 certainly one of the several desirable critical
8 features for diagnostic tests. Other being
9 specificity and uptake, also known as
10 utilization of a test.

11 BY MR. JONES:

12 Q If you turn to paragraph 40 of your declaration.

13 In this paragraph, you say -- starting on
14 the bottom of page 17: "By 2009, colonoscopy
15 was still the gold standard of CRC screening,
16 and most other implemented and experimental
17 alternatives not being able to provide
18 sufficient clinical value and patient benefits."

19 Sorry. I think I misread that.

20 Starting over.

21 By 2009 -- in this paragraph, you say, "By
22 2009, colonoscopy was still the gold standard of
23 CRC screening, with most other implemented and
24 experimental alternatives not being able to

1 provide sufficient clinical value and patient
2 benefits."

3 Is that right?

4 A Yes. That's right, yes.

5 Q When you are referring to "implemented
6 alternatives," what are you referring to here?

7 A So prior to 2009, the colonoscopy was just like
8 it says here: Colonoscopy was the gold standard
9 of CRC screening. It still is. It's both
10 diagnosed and therapeutic procedure. However,
11 one of the major problems was that most patients
12 at the time was not -- were not getting
13 colonoscopy as appropriate. And so there was a
14 significant interest in finding other ways to
15 screen besides colonoscopy. And several
16 techniques -- several approaches were tried.
17 One of them was flexible sigmoidoscopy. It's a
18 technique -- it's a probe-based technique in a
19 way -- in this way similar to colonoscopy, but
20 something that could've been done not by
21 gastroenterologists but by a more primary --
22 more primary care setting; for example, a
23 primary care physician.

24 In flexible sigmoidoscopy, a probe was

1 inserted in the sigmoid colon. So closer to the
2 rectum in as far as the descending colon. So we
3 were roughly looking at the distal third of the
4 colon.

5 If adenomas were found, then patient were
6 recommended to undergo colonoscopy, essentially
7 scoping the entire colon. The idea was to weed
8 out patients who don't need colonoscopy
9 necessarily but find patients who would benefit
10 from the full colonoscopy. Again, because most
11 patients did not get colonoscopy. This is one
12 of the techniques.

13 Another approach was radiological barium
14 enema. Another radiological approach that was
15 under development was CTC, or essentially a CT
16 scan-based colonoscopy, which at the time was
17 developed by GE.

18 There was a fecal occult blood test, of
19 course, available. FIT was available, immuno
20 fecal occult blood test was available as well.

21 These were the approaches that were
22 available at the time and practiced in clinic,
23 and these are the ones that I call
24 "implemented."

1 But none of them was good enough. None of
2 them was really shown to address the problem.
3 All those approaches had significant
4 limitations.

5 Flexible sigmoidoscopy was not very well
6 tolerated by patients either. Main PCPs did not
7 want to practice it for a variety of reasons.
8 It was lacking sensitive specificity as well
9 because you are looking only at one third of the
10 colon, usually, with this test.

11 CTC, despite significant investment from
12 GE, was lacking both sensitivity and specificity
13 as well.

14 A lot of, you know, the colon has a lot of
15 folds. Some of those folds were confused by the
16 algorithm and identified as polyps when there
17 were no polyps and vice versa.

18 Sensitivity was an issue as well, plus
19 patients still had to still undergo colon
20 preparation, bowel prep that nobody really
21 enjoys doing. And there was no anesthesia, so
22 patients still were -- it actually was more
23 painful than colonoscopy because of
24 insufflation. So that was -- that did not

1 really reach the sufficient sensitivity and
2 specificity.

3 Problems with FOBT and FIT are well known,
4 even though they were lower cost tests, but
5 uptake was hard to achieve as well because
6 patients did not like handling their stool.

7 And it was known at the time that the
8 diagnostic performance of FOBT and FIT, even
9 though there were better for actual colorectal
10 cancers, the numbers were very low for advanced
11 adenomas, which was understood at the time as
12 the gold standard endpoint that needs to be
13 detected in order for a test to be practically
14 used as a pretest, or what is known as a
15 first-tier screen test prior to colonoscopy.
16 And the undetectability of the lesions by FIT or
17 FOBT was fairly low, around 20th percentile
18 sensitivity.

19 The only other thing I would mention is
20 development of GI capsule, originally developed
21 for the esophageal cancer detection. It was
22 tested for lower GI tract cancers. It was very
23 difficult to use as well. Again, it had a lot
24 of problems with both sensitivity and

1 specificity.

2 So these were implemented tests. Every one
3 of them had significant problems. None of them
4 was really widely used. And so there was
5 significant research interest and commercial
6 interest in developing other alternative assays,
7 whether these are fecal tests or blood tests,
8 and I believe these are the ones I refer to as
9 experimental alternatives on page 18.

10 Exact Sciences Cologuard would become,
11 eventually, one of the tests that, to my
12 knowledge, is currently the only one that
13 actually made a difference for patients and is
14 making a difference today. At the time, it was
15 an experimental approach that eventually became
16 a highly successful solution.

17 Q So when you refer to experimental alternatives
18 in this sentence, what approaches are you
19 specifically referring to there?

20 A Primarily attempts of developing a test that
21 would be cost effective, would have good
22 utilization, and a good combination of
23 sensitivity, specificity that can be
24 administered prior to a colonoscopy.

1 Two major attempts -- two major directions
2 at the time were analysis of fecal matter and
3 analysis of blood biomarkers, primarily blood
4 proteins.

5 And based on the data that existed at the
6 time, there were no promising experimental
7 alternatives, as I believe the literature at the
8 time suggests. Different groups looked like --
9 looked at specific -- for example, relevant to
10 this case, fecal analysis. Different groups,
11 different investigators looked at gene
12 mutations, detection of gene mutations in the
13 stool. They did not lead to sufficient
14 diagnostic performance.

15 Certain methylation markers began to be
16 investigated as well, and they did not seem to
17 provide practically -- practically valuable
18 performance. These are the experimental
19 approaches.

20 Q And then the first sentence in paragraph 41, you
21 say, "This situation remained until the
22 introduction of the Cologuard test by Exact
23 Sciences."

24 Right?

1 A That's correct.

2 Q The Cologuard test was released in 2014; right?

3 A Correct. Yes.

4 Q So the situation you discuss above remained
5 until 2014?

6 A Yes. Until the study published in the New
7 England Journal of Medicine by Imperiale, where
8 the results of the Cologuard test were
9 announced.

10 Q The Cologuard test was released by Exact
11 Sciences; right?

12 A It was.

13 Q Do you know whether the invention claimed in the
14 '781 patent was invented by someone at Exact
15 Sciences?

16 MS. FERNANDS: Objection. Form.

17 THE DEPONENT: I can't testify -- I cannot
18 talk about the entire history of the patent.
19 I'm not familiar with the history of the patent.
20 What I do understand is that the primary
21 inventor of the patent, whose name you should
22 still teach me how to pronounce correctly.

23 BY MR. JONES:

24 Q Joost Louwagie.

1 A Louwagie?

2 Q That's my understanding, based on conversations
3 with Dutch colleagues.

4 A That's simple enough. Okay. Right. As far as
5 I understand, at the time of filing the patent,
6 he was not employed by Exact Sciences. And
7 Exact Sciences licensed the patent.

8 I'm not -- I don't have details -- other
9 details of the history of the patent.

10 What I do know is that -- what I do
11 understand is that if Imperiale publication on
12 Cologuard came out in 2014, that was a
13 significant -- it was very large at the time, by
14 the standards of the day, a very significant
15 study in terms of number of patients recruited
16 for the study. The recruitment and planning for
17 the study, the assay development, development of
18 the test must have occurred years prior to 2014.

19 So as far as I understand, Exact Sciences
20 had been working on combining FOBT with the
21 nucleic acid biomarkers for quite some time
22 prior to 2014.

23 Q In paragraph 41, you say, "Through the
24 combination of fecal DNA analysis and

1 identification of blood proteins in the stool"

2 -- sorry. Let me take a step back.

3 In paragraph 41, you say, "The Cologuard
4 test by Exact Sciences, which, through the
5 combination of fecal DNA analysis and
6 identification of blood proteins in the stool,
7 offered excellent sensitivity and specificity
8 for early stage CRCs and robust sensitivity and
9 excellent specificity for advanced adenomas."

10 Do you see that?

11 A Correct. Yes, I see that.

12 Q And then you say, "For example, Imperiale, et
13 al., recorded an article published in the
14 New England Journal of Medicine in 2014 that the
15 Cologuard test achieved 92.3 percent sensitivity
16 and 86.6 percent specificity for CRC."

17 A Uh-huh. Right.

18 Q The numbers you provide here are the sensitivity
19 and specificity of Cologuard for colorectal
20 cancer; right?

21 A Right.

22 Q And you consider the Cologuard's 86.6
23 specificity for colorectal cancer to be
24 excellent?

1 A I consider the combination of sensitivity,
2 specificity, as you said, 92 percent,
3 86 percent, especially at the time. But
4 excellent, yes. And, clearly, compared to any
5 other alternative even that existed at the time
6 or currently exists. I think that would be
7 excellent, yes.

8 Q Here, you don't say what Cologuard sensitivity
9 or specificity for advanced adenomas is, do you?

10 A Not in this paragraph, but in other parts of the
11 declaration, I believe I discuss that.

12 Q Where in your declaration do you provide
13 Cologuard sensitivity and specificity for
14 advanced adenomas?

15 A You know what, it would take me some time to
16 find where it is, but it's -- for sure those
17 numbers are listed in the reference itself, in
18 the abstract of the reference. The sensitive
19 for advanced adenomas was about 40 percent. I
20 think it was about 42 percent. And the
21 specificity was in the -- between the 80th
22 percentile, which constituted more than doubling
23 of sensitivity for advanced adenomas compared to
24 fecal occult blood test alone with a very

1 small -- I think a 5 or so percent drop in
2 specificity with the overall significant
3 increase in the -- at AUC, area under the curve.

4 You're correct. I don't mention those
5 numbers in this particular paragraph, but it
6 is -- it is prominently featured in the abstract
7 and throughout the text of that reference.

8 Q Why don't you mention the sensitivity and
9 specificity of the Cologuard test for advanced
10 adenomas here?

11 A When I was writing this, this paragraph, in
12 particular, talks about, as you understand, a
13 2014 paper that was published after the 2009 --
14 after 2009. So most of the discussion and
15 declaration focuses on what was happening prior
16 and what was known prior to 2009. So -- and it
17 is in the reference. That is mentioned. So
18 it's also one of those facts, as I think at this
19 point, fairly well-known to most people who
20 practice in the field that the sensitivity,
21 specificity for advanced adenomas were in the --
22 you know, about 40 percent and about 80 percent,
23 which was significant improvement over --
24 compared to essentially anything else that

1 existed at the time or, you know, still exists.

2 Q But in this paragraph, why did you choose to put
3 the sensitivity and specificity for colorectal
4 cancer but not the sensitivity and specificity
5 for advanced adenomas?

6 A I could have certainly talked about advanced
7 adenomas here. I don't think there was any
8 particular reason. I don't think there's a
9 reason to read through the lines here.

10 One thing that is -- that is very,
11 you know, clear and very well-known in the field
12 is that the gold standard endpoint of screening
13 should be advanced adenomas. And I think that
14 fact is repeated several times in my
15 declaration.

16 Q So if the gold standard endpoint for screening
17 is advanced adenomas, how come you -- in this
18 paragraph, you focused on Cologuard's
19 sensitivity and specificity for colorectal
20 cancer?

21 MS. FERNANDS: Objection. Form.

22 THE DEPONENT: This 2014 paper is not
23 the -- it's not directly relevant to what was
24 happening prior to 2009, which is the subject of

1 the declaration. That's why it's not discussed
2 in significant detail.

3 If I had a chance or belief that it would
4 be important to discuss that particular paper
5 extensively -- more extensively in this
6 declaration, for sure, I would talk about
7 advanced adenomas reported in this paper. It's
8 just not -- it's not pertinent to what was
9 happening prior to 2009, and the subject of the
10 obviousness of the patent, which was the focus
11 of my declaration.

12 If anybody is trying to read between the
13 lines and assume that because that particular
14 paragraph referencing the 2014 paper used CRCs
15 as an example of how good Cologuard test was, I
16 think it's just misreading of the -- of what
17 we're trying to say, what I'm trying to say
18 here.

19 This is just an example -- one of several
20 examples I could have given indicating that in
21 2014, the first paper referring to -- describing
22 a large validation trial on Cologuard was
23 published, which launched -- which eventually
24 launched -- allowed the Cologuard to be

1 launched.

2 The point here is that it happened in 2014.
3 The point of this paragraph is not to compare
4 Cologuard with something else. The point of the
5 paragraph is not comparison of Cologuard with
6 other solutions, other approaches, but to give a
7 date when the change happened. That's why it's
8 not discussed in any significant details.

9 If that was important to discuss Cologuard
10 in detail, I would talk about, of course, area
11 under the curve, the combination of sensitivity,
12 specificity. I would talk about uptake. I
13 would talk about sensitivity to -- specificity
14 to advanced adenomas, and as part of the latter,
15 specificity to advanced adenomas. I would talk
16 about high sensitivity and robust specificity
17 for sessile serrated polyps, which was
18 several -- not double. It was multiple times
19 higher than that of FIT alone. And the reason
20 that is important is because this particular
21 subtype of advanced adenomas are considered more
22 dangerous and faster growing. More aggressive
23 lesions, faster growing that would need to be
24 removed by colonoscopy urgently.

1 So colon cancer in advanced adenomas, and
2 particular subtypes of advanced adenoma, SSP,
3 that's what -- that, if the idea was to -- if
4 the goal were to compare Cologuard without
5 tests, these are the criteria that I would use
6 and explain this paragraph.

7 But, like I said, the goal of this
8 paragraph is to provide a date primarily. Colon
9 cancer was just an example.

10 So I would highly recommend not to read in
11 this paragraph what an interpreted -- I would
12 recommend not to read between the lines and
13 interpret it in a way that it was not written.

14 BY MR. JONES:

15 Q You rely on the performance of the Cologuard
16 test in support of your opinions on secondary
17 considerations, don't you?

18 A Correct.

19 Q So the performance of the Cologuard test was
20 relevant to the opinions you set forth in your
21 declaration; right?

22 A Yes.

23 Q So to the extent the Cologuard test was relevant
24 to the opinions you set forth in your

1 declaration, is there a reason why nowhere in
2 the declaration you give Cologuard's sensitivity
3 and specificity or advanced adenomas?

4 A Let me make sure it's not stated in other
5 places.

6 Q Okay.

7 A I think I agree with you. I don't see right now
8 if sensitivity and specificity of Cologuard for
9 advanced adenomas is explicitly stated in my
10 declaration.

11 I don't see that. I believe that you
12 carefully read it. So, yeah, I do not see it
13 here.

14 So your question is: "Why is it that it's
15 not listed?"

16 Q My question is: Why do you give the sensitivity
17 and specificity of Cologuard for colorectal
18 cancer but nowhere do you give the sensitivity
19 and specificity of Cologuard for advanced
20 adenomas?

21 A Right. Well, so if you look at the section on
22 Secondary Considerations -- I think it's page
23 63 -- I do not believe that in that section I
24 listed or discussed specificity of Cologuard for

1 CRCs either. So I don't think in this section
2 the sensitivity and specificity of Cologuard are
3 listed for either CRCs or advanced adenomas.

4 The place where sensitivity and specificity
5 are listed is the one that you pointed out.
6 It's the one of introductory. It's the
7 introductory paragraph, which is 41. And
8 that's -- that's the place where CRCs are listed
9 as just an example. That's not the -- it's not
10 the point of this paragraph, as you can see, to
11 compare this performance with anything else.
12 There's no other comparison. We're not
13 listing -- we're not talking about FOBTs or
14 something else, or other experimental
15 approaches.

16 It's just an indication that in 2014,
17 Cologuard became available, and that changed the
18 landscape of colorectal cancer screening.

19 The reason I'm pointing this out is -- I
20 think it is important that where CRCs are
21 mentioned, CRCs are not the point of the
22 paragraph. It's the date. It's the fact that
23 Cologuard became available. That is the point.

24 The section on secondary considerations

1 that you're referring to does not talk about
2 performance of Cologuard at all. It does talk
3 about performance of other tests. It does not
4 talk about performance of Cologuard, either CRCs
5 or adenomas.

6 The performance of Cologuard is, at this
7 point, is well-known. It is in the reference.
8 It is in the abstract of the reference. I
9 believe that is the reason why it was not
10 mentioned.

11 I could have written about it. There's no
12 question. I could have. And if my point was to
13 discuss specifically performance of Cologuard as
14 it happened after 2009, I can assure you I would
15 absolutely talk about CRCs, adenomas, and I
16 would probably emphasize this piece as well.

17 Q But that's not something you discussed in your
18 declaration?

19 A I did not discuss it in the declaration because
20 that was not the focus of the section on
21 secondary considerations.

22 But I do want to emphasize that I, in my
23 opinion and in the opinion of most people in the
24 field prior to 2009 and after, the primary

1 endpoint of pre-colonoscopy screening, such as
2 Cologuard or any other, has to be advanced
3 adenomas.

4 And maybe we can take a very quick step
5 back here because that is -- I think it is an
6 important point that people -- people who are
7 not familiar with the subject matter might be
8 somewhat confused about it.

9 So when we talk about colonoscopy
10 screening, even the word "screen" shows up.
11 Really, what colonoscopy is, it's both
12 diagnostic and therapeutic procedure. When an
13 endoscopist does a colonoscopy, they identify
14 location of adenomas, and they are removed at
15 the time of colonoscopy. So it's essentially a
16 curative procedure and diagnostic procedure in
17 one.

18 Importantly, colonoscopy cannot address
19 colorectal cancers. That is done by colorectal
20 surgeons. It's an invasive surgery. It's a
21 major surgery frequently followed by
22 chemotherapy or radiation or a combination,
23 chemo/radiation. It has a completely different
24 survival profile. Because as soon as you

1 develop actual cancer, there is always a chance
2 that even if it's an early cancer, the cells
3 might have penetrated -- some cells might have
4 penetrated basement membrane. They might end up
5 in lymph nodes, even if we don't necessarily
6 radiologically see them clinically.

7 In a lot of cases, you can do surgery,
8 chemo/radiation, and 5, 10 years later, patients
9 may come back with a recurrence or metastasis in
10 a different organ. So having a colon cancer is
11 a completely different ballgame than having
12 precancerous lesions. So that is why what's
13 relevant for colonoscopy is to identify and
14 remove precancerous polyps or adenomas, such as,
15 let's say, flat or depressed lesions as well.
16 Identify and remove.

17 So, therefore, any test that might precede
18 colonoscopy has to have reasonable sensitivity
19 and, of course, you know, practically reasonable
20 specificity for precancerous lesions.

21 The question, which ones? Which lesions
22 are clinically significant?

23 So definition of clinical significance is
24 that a lesion has to have significant chance of

1 progression into a tumor. And it can be an
2 actionable lesion as well that can still be
3 easily treated. So much earlier, smaller
4 adenomas, they have a lower rate of progression.
5 Typically below 1 percent -- well below
6 1 percent. Many of them even regress on their
7 own, and they're not considered clinically
8 significant because most of them do not amount
9 to actual tumor.

10 Advanced cancer circulate. Colonoscopy
11 does not deal with cancers, but advanced
12 adenomas are kind of in a sweet spot. They have
13 significant rate of progression. It's depending
14 on their attributes and location and molecular
15 characteristics and gender, they vary anywhere
16 from several percent progression per year to
17 10 percent progression per year that amounts to
18 over -- an average, over 40 percent chance of
19 progression over 10 years, which is the
20 colonoscopy interval. So this is due to a
21 clinically significant lesion. It also has
22 reasonable prevalence, about 7 percent.

23 That's why, you know, well before 2009,
24 most experts in the field, most professionals in

1 the field, most adviser bodies had -- in
2 recommending advanced adenomas, as the gold
3 standard endpoint for colonoscopy prescreening
4 or diagnostic tests.

5 That's why I just wanted to clarify this.
6 This is, indeed, a very important point.
7 Advanced adenomas are and should be the gold
8 standard of screening.

9 Q You'll agree with me that if a patient does have
10 colorectal cancer, they would be better off if
11 that colorectal cancer was detected; right?

12 MS. FERNANDS: Objection. Vague.

13 THE DEPONENT: I think you're asking if a
14 patient has colorectal cancer, they would be
15 better off if it's detected versus not detected
16 at all by any means?

17 BY MR. JONES:

18 Q Yes.

19 A For sure. Clearly, if cancer is too late, it's
20 a later-stage cancer, it probably would have
21 symptoms. It would detect based on symptoms.
22 And, as we know, the chance of survival time
23 goes significantly down with the later the
24 disease is.

1 So I do agree with you that detecting colon
2 cancer early versus not detecting it at all is
3 clearly a good thing.

4 Q Okay.

5 A Having said that, I do want to point out that
6 any test that actually detects the cancer has to
7 have several attributes that are crucial for its
8 clinical impact.

9 Ability to detect a disease, such as
10 cancer, sensitivity, is one of them. Very
11 important. Specificity is very important. And
12 uptake as well.

13 I would say three things are most critical.

14 Q Okay. So I'm giving you what is Exhibit 2008,
15 which I believe is the 2014 Imperiale study you
16 were mentioning.

17 A Uh-huh.

18 (Exhibit No. 2008 marked.)

19 BY MR. JONES:

20 Q This paper that's Exhibit 2008 is the Imperiale
21 paper that you cite to in paragraph 41 of your
22 declaration; right?

23 A Correct.

24 Q This paper is a large clinical study of

1 Cologuard?

2 A Correct. Yes.

3 Q The study was also called, I believe, the deep
4 sea study?

5 A I believe so.

6 Q Do you recognize that several of the co-authors
7 of this paper were Exact Sciences' employees?

8 A I would not be able to identify every one of the
9 co-authors and tell you whether they are -- they
10 work with Exact Sciences or not. But I do
11 recognize several names, yes.

12 Q Several names as Exact Sciences' employees?

13 A Exact Sciences, yeah. I recognize several
14 names, people who are Exact Sciences' employees.

15 Q If you go to page 10 of -- I'm going to use the
16 pages on the top of it, where it says, "Patent
17 Owners." Exhibit 2008, if you go to page 10.

18 At the very end --

19 A Uh-huh.

20 Q You'll see that this study was supported by
21 Exact Sciences.

22 A I see that, yeah.

23 Q Will you agree with me when the Imperiale paper
24 refers to a multi-target stool DNA test, it's

1 referring to Cologuard?

2 A I believe so.

3 Q So if you turn back to the first page, under the
4 Results section, you'll agree with me that -- it
5 says -- I guess the second sentence -- that the
6 sensitivity for detecting colorectal cancer was
7 92.3 percent with Cologuard and 73.8 percent
8 with FIT; right?

9 A Let me just find the exact line.

10 Yes. Correct. Yes. 92.3 percent of the
11 DNA testing and 73.8 percent with FIT, yes.

12 Q And you'll agree with me, when it's saying "DNA
13 testing," it's referring to Cologuard here?

14 A Yes.

15 Q So Cologuard was more sensitive than FIT for
16 colorectal cancer; right?

17 A Correct.

18 Q Will you agree with me that this higher
19 sensitivity of Cologuard than FIT for colorectal
20 cancer is an advantage for Cologuard?

21 A It is.

22 Q And then the next sentence says, "The
23 sensitivity for detecting advanced precancerous
24 lesions was 42.4 percent with DNA testing and

1 23.8 percent with FIT."

2 Do you see that?

3 A I see that, yes.

4 Q Will you agree with me that advanced
5 precancerous lesions would include advanced
6 adenomas?

7 A Yes, it would.

8 Q So Cologuard detects less than half of patients
9 with advanced precancerous lesions that were
10 tested?

11 A Yes, it does. Yes, based on this 42.4 percent.
12 Yes, a little less than half. Yes.

13 Q And if you go two-thirds of the way down, you'll
14 see a sentence that starts with "Specificities."

15 A The sentence starts with -- yes, "Specificities
16 with DNA testing."

17 Okay. I see that.

18 Q It says, "Specificities with DNA testing and FIT
19 were 86.6 percent and 94.0 percent
20 respectively."

21 Right?

22 A Yeah, I see that.

23 Q So you'll agree with me that the FIT test had a
24 higher specificity for colorectal cancer than

1 Cologuard; right?

2 A Yes, it did.

3 Q If you look at the "Conclusion" sentence?

4 A Uh-huh. The last sentence?

5 Q Sorry. There's a section that says
6 "Conclusion," and there's a sentence there.

7 A Okay. Yeah, yeah.

8 Q This sentence says, "An asymptomatic person's
9 average risk for colorectal cancer, multi-target
10 stool DNA testing detected significantly more
11 cancers than did FIT that had more false
12 positive results."

13 Do you see that?

14 A I see that, yeah.

15 Q This conclusion sentence doesn't mention
16 Cologuard's ability to detect advanced adenomas,
17 does it?

18 A I believe it does -- yeah, it does not talk
19 about advanced adenomas here. This sentence
20 mentions cancers. It does not mention advanced
21 adenomas.

22 Q Would you agree with me that the Cologuard test
23 is not more convenient than a FIT test?

24 MS. FERNANDS: Objection. Form.

1 THE DEPONENT: Would you mind rephrasing
2 the question? I don't want to get confused by
3 double negative.

4 BY MR. JONES:

5 Q Let me -- I'll restate the question.

6 A Thank you.

7 Q Is the sample collection process for the
8 Cologuard test more convenient than the sample
9 collection process for a FIT test?

10 A I don't believe they discuss or provide -- I
11 don't believe they provide data comparing
12 patient -- how a patient felt about collecting
13 FIT samples versus Cologuard samples. So I
14 can't really provide opinion on that.

15 Based on the fact that some handling of the
16 stool was required to do Cologuard, I would
17 expect it to be somewhat similar to patients'
18 compliance with FIT. But I think the exact
19 answer to your question also depends on what
20 kind of FIT procedure we are considering. In
21 some prize studies, people were required to --
22 patients were required to refrigerate their
23 samples. That would presumably add a more
24 complexity and inconvenience. Nobody wants to

1 put their stool in the fridge. But I don't
2 believe that was a required step here.

3 So from this perspective, I would expect it
4 to be somewhat along the lines -- inconvenience
5 would be similar between Cologuard and FIT. But
6 like I said, they don't provide -- I don't
7 believe they provide actually survey data on
8 that.

9 Q Aside from its higher specificity for colorectal
10 cancer and advanced precancerous lesions, are
11 you aware of any advantages Cologuard has over
12 FIT tests?

13 MS. FERNANDS: Objection. Form. You might
14 want to look at how you asked that question. I
15 think you used the wrong word in your question.

16 BY MR. JONES:

17 Q Oh, I did. Thank you for specifying.

18 Okay. Let me rephrase.

19 Aside from higher sensitivity for
20 colorectal cancer and advanced precancerous
21 lesions, are you aware of any advantages
22 Cologuard has over FIT tests?

23 A I would say that the major advantages of
24 Cologuard versus FIT would be the -- precisely

1 the combination of sensitivity and specificity.

2 In biostatistics, in biomarker field, a
3 performance of a test is -- the whole
4 performance of a test is most accurately
5 assessed by what is known as the Receiver
6 Operator Curve, or ROC. Some people call it
7 "ROC curve." And I believe there are examples
8 of this kind of data in this paper, unless I'm
9 mistaken. Yes.

10 I think if we look at figure 3, they show a
11 couple of examples.

12 These are the kind of analysis -- this is
13 the kind of analysis that is typically used
14 in -- when evaluating the performance of a test.
15 And the reason this is important is because it
16 takes into consideration the balance between
17 sensitivity, specificity. The exact value of
18 sensitivity and specificity, it depends on a
19 specific cutoff point of the curve. So each
20 test may have serious sensitivities and
21 specificities. And that curve captures all of
22 them.

23 So what we can see here is that for both
24 colorectal cancers, which is panel A -- figure 3

1 panel A and advanced neoplasia, panel B, the ROC
2 curves are clearly better. The ROC curves of
3 the Cologuard are better than FIT. And this is,
4 in particular, captured by one statistic that is
5 perhaps the most critical statistic of any
6 diagnostic test when we refer to its
7 performance, which is Area Under the Curve, or
8 AUC. And, again, they are better for --
9 significantly higher for Cologuard versus FIT.

10 So I would say this, to me -- to me, from a
11 biomarker perspective, from a scientific
12 perspective, this is the -- I would say this is
13 the major advantage of Cologuard test versus
14 FIT.

15 A consequence of that is that because the
16 ROC curve is better, one can find a cutoff point
17 where the sensitivities and specificities are
18 optimized. And what they did here in this work,
19 in the Imperiale paper, they got a cutoff point
20 that had a small drop in specificity. I believe
21 a, what, 8 percent, 7, 8 percent drop compared
22 to FIT, but major increase in sensitivity.

23 The increase in sensitivity for cancers is
24 sizable. It's almost 20 percent, from 73.8 to

1 92.3 percent. But I would say, more
2 importantly -- or more impressively, I would
3 say, there is almost doubling of sensitivity for
4 advanced adenomas, again, for a marginal drop in
5 the specificity.

6 An even more impressive increase in
7 sensitivity for serrated sessile polyps
8 measuring one centimeter or more, FIT had
9 sensitivity by about 5 percent, which is, as you
10 can imagine, it's very low. It's almost as good
11 as tossing a coin literally. It's almost a
12 random chance sensitivity.

13 And the sensitivity of Cologuard is 42.4 --
14 I believe it's 42.4 percent. So it's a multiple
15 of FIT. And that is -- I think it's very
16 important as well because these are the lesions
17 that are also harder to detect. They are more
18 aggressive.

19 So the good summarize, I think it's a
20 sizable increase in sensitivity for cancers. A
21 major increase for advanced adenomas and major,
22 major increase for serrated sessile -- sessile
23 polyps, with a marginal drop in specificity,
24 which still makes the best clinically valuable.

1 But, again, to me, the heart of the matter
2 is figure 3 in the fact that the ROC curve, the
3 overall performance of the test that
4 incorporates both sensitive and specificity is
5 significantly better than that of FIT.

6 So as a scientist, that's what I would
7 focus on.

8 If -- from the -- yeah. So, to me, that's
9 what I would focus on. To me, these are the
10 major advantages. And it is -- and I am sorry
11 to keep going back to this.

12 Again, we have to put this in good context,
13 this paper into context of what was happening at
14 the time. And at the time, we, in the field,
15 did not have a test that would have such high
16 sensitivity with a clinically acceptable
17 specificity for advanced adenomas. That, to me,
18 is the -- that, to me, is the -- is a big deal
19 here.

20 Q When you say "at the time," are you referring to
21 2014?

22 A I'm referring to 2014. And, you know, frankly,
23 even today, this is currently it's the only test
24 that I'm aware of that is -- has been

1 implemented in clinical practice that has this
2 kind of sensitivities and specificities for
3 advanced adenomas, despite multiple, multiple
4 efforts of other companies and other
5 investigators to come up with a better test.

6 They pretty much all failed. So not for a
7 lack of trying. So this situation existed in
8 2009, 2014, and even today.

9 Q Okay. If you look at page 3.

10 A The same reference?

11 Q The same reference.

12 A Okay.

13 Q You'll see there's a paragraph that under the
14 heading Primary and Secondary Outcomes.

15 A Yes, I see the paragraph.

16 Q The first sentence says, "The primary outcome
17 was the ability of the DNA tests to detect
18 colorectal cancer, i.e., adenocarcinoma with
19 disease stage determined with the use of the
20 American Joint Committee on Cancer, AJCC staging
21 system."

22 Do you see that?

23 A I see that.

24 Q So the primary outcome of the Cologuard clinical

1 trial described in the Imperiale 2014 paper was
2 the ability to detect colorectal cancer; right?

3 A It is, yes. It is the primary outcome. We have
4 to understand what the sentence means, what
5 primary outcome means. The primary outcome of a
6 clinical trial is the endpoint for which
7 clinical trial is powered. If there is another
8 endpoint, that would, for example, be more
9 prevalent. So it's not powered for that
10 endpoint, but it's automatically overpowered for
11 that endpoint. That becomes the secondary or
12 tertiary endpoint. So the -- so here's how the
13 numbers work out. The prevalence of colorectal
14 cancer in general population is about
15 .7 percent. Prevalence of advanced adenomas is
16 about 7 percent. So cancer, 0.7; adenomas 10
17 times more, 7 percent.

18 The way this study was conducted was a most
19 robust way colorectal cancer study can be
20 conducted. You do a multi-center study, you
21 recruit patients who undergo a colonoscopy. So
22 anybody who is eligible for a colonoscopy,
23 recruit them. It means you are dealing with
24 your eligible population.

1 In order to power the study, to have
2 statistical power to say whether your AUC,
3 sensitivity, specificity, or other performance
4 metrics are statistically significantly superior
5 to those of a comparator test, or just define
6 them accurately enough within a certain range,
7 you have to have a certain number of cases.

8 So what's done in clinic -- any clinical
9 trial of the sort is you first figure out how
10 many cases you would need in order for the study
11 to be powered enough.

12 And you have to do it for the least
13 prevalent -- in a study design like that, in a
14 prospective trial like that, you have to power
15 the study for the least prevalent condition,
16 because that determines the number of subjects
17 that you need to recruit.

18 In this case, it would be colon cancers
19 because of their low prevalence of 0.7 percent.

20 As soon as you recruit enough patients to
21 power the study for colorectal cancers, you
22 automatically satisfy the requirement to power
23 the study enough for advanced adenomas because
24 they are 10 times more prevalent, which in the

1 language of clinical trials means that it
2 becomes a -- colon cancers will be the primary
3 outcome; advanced adenomas would be secondary
4 outcome.

5 Q So if you go to page 2 of the paper, the last
6 paragraph of the -- I guess it would be the
7 Introduction section.

8 A The one that starts "This study"?

9 Q Yeah.

10 A Right. Okay.

11 Q It says, "In this study, we evaluate the
12 multi-target stool DNA test as a tool for
13 screening."

14 A Wait. I'm probably looking at the wrong --

15 Q Sorry. It's right above the Method section?

16 A Okay. Okay.

17 Q That paragraph.

18 A Okay. It's just the last paragraph on that
19 page. Also is this study.

20 Q Yes.

21 A In the study. Okay.

22 Q "In the study, we evaluate the multi-target
23 stool DNA test as a tool for screening."

24 Then it says, "The primary aim was to

1 determine the performance characteristics of the
2 DNA test in the detection of colorectal cancer."

3 Do you see that?

4 A Correct. It says that. And then it says, "The
5 secondary aim" -- "The secondary aims were to
6 determine the performance of the DNA testing,
7 the detection of advanced precancerous lesions."

8 Right. I see that.

9 Q So the primary aim was to determine the
10 performance characteristics of the DNA test,
11 which is Cologuard, in the detection of
12 colorectal cancer; right?

13 A That is correct. And I think what you are
14 referring to is analogous to what we just talked
15 about. So in the language of clinical trials,
16 you design an aim based -- or outcome or your
17 primary endpoint based on what you need to power
18 the study for because that determines how many
19 patients you need to recruit.

20 So these words were used independently.
21 It's just the language of how people talk about
22 clinical trials. So it's a -- what this
23 means -- this paragraph means that they had to
24 power the study to identify the least prevalent

1 condition, which is cancer. And by default,
2 advanced adenomas become the secondary endpoint.

3 This is just a nomenclature of the language
4 of describing clinical studies. And they did
5 the appropriate thing.

6 In any clinical study, in a clinical trial
7 of this sort, if you want to use this data for
8 regulatory approval, for example, you would have
9 to show that you can detect both advanced
10 adenomas and cancers. You can also show that
11 you can detect just advanced adenomas. Your
12 study has to include cancers.

13 Q Why does your study have to include cancers?

14 A This is just a normal procedure, standard
15 procedure of FDA and other bodies, that you
16 cannot make -- you would not be able to make a
17 claim that you can detect colon cancers unless
18 you show that you can detect colon cancers.

19 If you can only show that you can detect
20 advanced adenomas, you can -- you still have to
21 show that you can detect cancers, even though it
22 logically makes sense. I understand logically
23 it makes sense if you are -- if your test is
24 good enough to detect early lesions, most people

1 would intuitively assume that the test should be
2 good for later stage lesions, but that's not how
3 medicine works. You have to prove every
4 statement you make.

5 So you would have to prove that -- you have
6 to show results for cancers and advanced
7 adenomas in your trial. And because it's a
8 prospective trial -- again, they recruit
9 patients who come in for a colonoscopy. They're
10 not specifically going to a patient who is known
11 to have cancer, or known to have an adenoma and
12 then it can just pick and choose. It's called
13 case control study.

14 They had to do a large study to have enough
15 patients who were cases -- who had cancers
16 because of the prevalence of about .7 percent.

17 And that is why this is -- that study had
18 to recruit almost 10,000 patients, because when
19 you recruit 10,000 patients, you would,
20 you know, less than 1 percent of the patients
21 would be cancers. And we see this in these
22 numbers. Let's say 60, if they had in the
23 abstract. The Result section to say our -- they
24 recruited 9,989 participants, 65.7 percent. So

1 it's very close to what was -- what the
2 prevalence is. .7 percent had colorectal
3 cancer. 7 out of 57, 7.6 percent had advanced
4 adenomas.

5 Again, all these numbers are very close to
6 what is known about the prevalence of this
7 disease in population. They estimated, based on
8 power calculations, based on the projection of
9 what sensitivity, specificity might be, what the
10 variability of biomarkers across the population.
11 So they look at all that, and they estimated
12 that they need around 65 cases. That means that
13 they have to have at least 65 colorectal,
14 approximately, colorectal cancers, which
15 translate into 10,000 patients. So colorectal
16 cancer becomes the primary aim of the study.

17 If the primary aim of the study were to
18 detect -- if they did not have to look at
19 cancers at all, the least prevalent condition,
20 whatever it might be, would become the primary
21 aim or primary outcome or primary endpoint. So
22 you always power the study for the least
23 prevalent case, and that becomes your primary
24 aim of the study. It does not mean that your

1 secondary aim is not important. It's not a
2 statement of importance. It's a statement of
3 statistics.

4 Q Would you agree that both aims were probably
5 important?

6 MS. FERNANDS: Objection. Form.

7 THE DEPONENT: I think there is a nuance in
8 nomenclature. When we colloquially use the word
9 "aim" -- when most people say "aim," they assume
10 something that they want to achieve. But in
11 research and clinical trials, aim has double
12 meaning. It's certainly used all the time in
13 this conventional colloquial sense as our goal;
14 right? This is what we would like to show --
15 like to do. Used all the time.

16 And also in the language of clinical
17 trials, it's also used from the -- to indicate
18 what we are powering the study for. It is in
19 this context, that word "aim" is used in the
20 last paragraph of the introduction.

21 And the reason -- the reason for this kind
22 of language, why the word "aim" is used, is
23 because, based on the number of cases, you have
24 to identify how many patients you need to

1 recruit. And so that now -- it turns out to be
2 10,000 patients.

3 So that's why it's an aim; otherwise, if
4 they -- if the aim was different, you could get
5 away with a different number of patients, or
6 maybe you would have to have -- recruit more.

7 So we just -- this terminology nuance in
8 the word "aim," so from the perspective of
9 clinical trial design, I think the word "aim"
10 here is used appropriately.

11 Now, if your question refers to the word
12 "aim" as understood as in a more colloquial,
13 more intuitive sense, what they would like to
14 show in the study, would it be important for
15 them to show that their test works well for
16 cancers, as well as advanced adenomas?
17 Absolutely. The answer is "yes."

18 It's not a secondary aim in a colloquial
19 sense. Right?

20 And I think we see this pretty clearly,
21 pretty much in a lot of places throughout the
22 paper. They talk about both CRCs and adenomas.
23 We see this in advanced adenomas. We see this
24 in the results. We see this in the way the

1 report -- the data.

2 We see careful analysis in figure 2 of the
3 sizes of advanced adenomas that they had in this
4 study, which is an important consideration on
5 its own.

6 Figure 3, the report -- the performance of
7 the test, they show ROC curves for both cancers
8 and adenomas. They really go hand in hand,
9 talking about both.

10 So from the intuitive use of the word
11 "aim," I would say that when I read this paper,
12 it was clear to me that they understand that
13 both aims -- quote, unquote -- colloquial aims,
14 advanced adenomas and cancers are equally
15 important.

16 In the end of the day, I think they
17 understood quite well that what's going to make
18 the test practical or not is whether the test
19 has good accuracy for advanced adenomas.

20 MR. JONES: Okay. So we have been going
21 more than an hour. It's 12:21.

22 Can we just go off the record?

23 (Break.)

24 \\\

1 BY MR. JONES:

2 Q Dr. Backman, I'm giving you a paper, which is
3 Exhibit 1004 of this IPR.

4 Do you recognize this document?

5 A I do, yeah.

6 (Exhibit No. 1004 marked.)

7 BY MR. JONES:

8 Q Do you recognize this as a paper by Lehnard, et
9 al., titled "Analysis of Promoter Methylation in
10 Stool, a Novel Method for Detection of
11 Colorectal Cancer"?

12 A I do.

13 Q And if you turn to paragraph 55 in your
14 declaration on page 23.

15 A 55; right?

16 Q Yep.

17 A Yeah, I see that.

18 Q And this Lehnard paper I gave you is the paper
19 that you discussed in this section, beginning at
20 paragraph 55; right?

21 A Correct.

22 Q In the Lehnard paper, the authors tested stool
23 samples for both a DNA methylation marker and
24 for blood proteins; right?

1 A Yes.

2 Q And the DNA methylation marker that was tested
3 for here is HIC1 methylation?

4 A That's correct.

5 Q And if you go to Table 1 in Lehnard, which is
6 on, I believe, the second page of the document.

7 A Uh-huh. Yes, I see that.

8 Q This table provides DNA methylation and blood
9 protein assay results for individual patients in
10 the study; right?

11 A Yes.

12 MS. FERNANDS: Objection. Form.

13 BY MR. JONES:

14 Q And you'll agree with me that the blood protein
15 test detected colon cancer in samples in which
16 the DNA methylation test did not?

17 MS. FERNANDS: Objection. Form.

18 THE DEPONENT: The FOBT detected -- FOBT
19 came out positive in some of the patients that
20 had a negative HIC1 methylation marker.

21 BY MR. JONES:

22 Q And all the patients in Table 1 actually had
23 colon cancer; right?

24 A I believe so.

1 Q In this table, the DNA methylation marker
2 detected colon cancer in samples where the FOBT
3 test did not?

4 A I'm sorry. Can you repeat the question?

5 Q This table also shows that the DNA methylation
6 test detected colon cancer in samples where the
7 FOBT test did not; right?

8 A That's right. So some of the FOBT patients --
9 some of the FOBT negative patients had positive
10 HIC1 methylation. I agree with that, yes.
11 That's what this table shows.

12 Some of them had both markers negative;
13 some of them had both markers positive. But
14 some patients who had FOBT negative were HIC1
15 positive.

16 Q On the same page as Table 1, on the bottom
17 left-hand column, at the end, they note that --
18 the authors note that, "We show that HIC1
19 promotor methylation can be detected frequently
20 and with high specificity in stool samples from
21 patients with colorectal cancers."

22 Do you see that?

23 A I see that.

24 Q And then they also say that, "The combination of

1 HIC1 methylation analysis with FOBT allowed for
2 the detection of two-thirds of colorectal
3 cancers."

4 A Yeah, I see that. Yes.

5 Q If you go to page 147 of the paper.

6 A Yes, I'm here.

7 Q You'll see in the paragraph right above the
8 discussion, second to the last sentence, the
9 authors state that, "The combination of both
10 assays resulted in increased detection rate for
11 colorectal cancers."

12 Right?

13 A Yes. I see that.

14 Q So here, the authors specifically call out that
15 the -- when you use both the DNA methylation
16 test and FOBT test, it resulted in increased
17 detection rates for colorectal cancer; right?

18 A Yeah, I see that. Yes.

19 Q If you go to the Materials and Methods section,
20 which is on page 143 of the paper, the second
21 paragraph starts with, "Stool samples were
22 collected before cathartic preparation for
23 scheduled surgery or colonoscopy."

24 A Uh-huh. Right.

1 Q And then it says -- in the last sentence of this
2 paragraph, it says, "Samples were received
3 within 10 hours after defecation in the
4 laboratory, aliquoted, and stored at -80°C."

5 Right?

6 A Right.

7 Q So you agree with me that this sentence explains
8 that the samples were received in the laboratory
9 within 10 hours of defecation; right?

10 A Right. I believe that's what they say, yes.

11 Q And the samples weren't frozen until they were
12 received at the laboratory; right?

13 A Correct.

14 Q And before the samples were frozen, they were
15 aliquoted; right?

16 A That's my interpretation too, yes.

17 Q That means that the fecal samples were divided
18 into multiple portions before being frozen at
19 the laboratory?

20 A Yes.

21 Q If you go to page 145. In the right-hand
22 column, there's a section called "Fecal Occult
23 Blood Testing."

24 A Right.

1 Q You'll agree with me that the fecal occult blood
2 test using the Lehnard study was a guaiac fecal
3 occult blood test?

4 A Yes, I agree.

5 Q And you'll agree with me that the samples were
6 subjected to the fecal occult blood test before
7 they were frozen; right?

8 A I think so.

9 Q So after the fecal samples were received at the
10 lab but before they were frozen, a portion of
11 the fecal sample was removed and tested in the
12 fecal occult blood test; right?

13 A Yes, I think so.

14 Q And then the remaining -- or some part of the
15 remaining portion of the fecal sample was tested
16 for the DNA methylation assay?

17 A Right. I think what -- yeah. I think what
18 they're doing is they receive a sample. They
19 aliquoted it. Part of it was used for FOBT, and
20 part of it was frozen.

21 Q And then the frozen part was tested for DNA
22 methylation?

23 A Yes. It appears that it was a one-center study,
24 so they -- that's why they were able to get

1 samples so quickly, within 10 hours. So it
2 looks like it was done -- I think the protocol
3 was the patients come to a lab. They say,
4 "Stool samples were collected before preparation
5 for surgery colonoscopy."

6 So it's probably a hospital setting,
7 clinical setting. They come in there. They
8 defecate. Samples are collected and brought for
9 analysis pretty much right away. Aliquoted.
10 Part is analyzed for FOBT, and not the part of
11 the aliquoted samples. I don't know how many --
12 how many aliquots they created. I don't know if
13 they say that, but one of them is analyzed for
14 DNA. I think that's the protocol they use. At
15 least this was my understanding.

16 Q If you go to the final page -- or the final page
17 of the body of the paper, which is on page 148.

18 A Uh-huh.

19 Q You'll see there's a section that begins, "In
20 summary"?

21 A In summary, the last paragraph?

22 Q Yes.

23 A Yes, I see that.

24 Q It says, "In summary, the section shows that

1 HIC1 is a sensitive and specific marker
2 well-suited for stool-based colorectal cancer
3 screening."

4 And then the next sentence says,
5 "Combination of HIC1 with a few additional
6 sensitive and specific methylation markers may
7 allow for highly sensitive and specific
8 stool-based detection of CRC and adenomas."

9 A I see that, yes.

10 Q This paragraph doesn't exclude the use of FOBT
11 in combination with the HIC1, does it?

12 A Well, I'm not entirely sure what it means to
13 exclude it. So in a sense, it doesn't exclude
14 FOBT in a sense that it doesn't say that HIC1
15 should not be -- should never be used with FOBT.
16 It doesn't say that.

17 So it doesn't exclude it explicitly.

18 I would have to say, however, that the
19 second sentence we just read, the combination
20 of -- the first sentence says HIC is a
21 reasonably good marker, right. Translated, in
22 colloquial language, that's what they're saying.

23 The second sentence says, "A combination of
24 HIC1 with a few additional methylation markers

1 may allow for the highly sensitive and specific
2 test."

3 So what they did in this paper, they
4 compared HIC1 alone, FIT alone, and their
5 combination, and they came to a conclusion,
6 which is stated here and also in the abstract
7 that HIC1 should be combined with methylation
8 markers.

9 So even though the sentence does not
10 explicitly mention it, and because it doesn't
11 mention it does not explicitly exclude FOBT in
12 the context, the sentence means that based on
13 the findings of the study, HIC1 should be -- the
14 next step of exploration should be to combine
15 HIC1 with methylation markers and not with FOBT
16 markers. Because they tested for that, and it
17 did not seem to be promising. That is my
18 reading of this -- of the conclusion of this
19 paper.

20 Q Where did they say that the combination of
21 markers did not seem to be promising?

22 A They do not say in the -- they do not say this
23 explicitly in this paragraph. The reason I --
24 that is how I would read this paper, and I think

1 most people in the field would read this paper
2 this way, because -- well, several reasons.

3 First, they tested HIC1 in combination with
4 FOBT. They analyzed the performance
5 characteristics, and their conclusion is that a
6 better approach -- next step should be to
7 combine HIC with other methylation markers. So
8 you explore option A. You see that it's
9 probably not very promising. Your conclusion is
10 you have to go B.

11 Now, why is that -- why is that that made
12 this conclusion? Why is that I, when I read
13 this paper myself, I actually came to the same
14 conclusion?

15 And, by the way, when I typically read
16 papers, I try not to read conclusions. I try to
17 look at the data first and make my own
18 conclusions. And then I compare my conclusions
19 with the conclusions of the authors to see if
20 they felt this way.

21 There are several reasons. One of them is
22 though -- although there was an increase in
23 sensitivity, as you mentioned, when HIC1 was
24 combined with FOBT and the test was able to

1 detect two-thirds of CRCs, which was higher than
2 FOBT or HIC1 alone, that coincided with a drop
3 in -- significant drop in specificity for
4 cancers as well.

5 Perhaps, at least equally importantly, is
6 we have to look at the statistics behind this
7 data. As I mentioned in the past, sensitivity
8 and specificity are just results of one
9 particular cut of -- of a diagnostic test. And
10 it is hard to make an assessment whether one
11 test is better than another just by looking at
12 sensitivity and specificity alone when -- if
13 there's some balance of the two. We need to
14 look at other statistics.

15 They don't talk about -- specifically, they
16 don't talk about areas under the curve and ROC
17 curve. Although this data can be extracted,
18 based on the data they provide because in this
19 small study, they're kind enough to provide
20 tables like Table 1 and Table 3 and Table 2,
21 where they'll list values -- essentially values
22 of markers for each and every patient.

23 So this data can be reanalyzed, and
24 characteristics, such as the values of AUC,

1 could you be calculated.

2 Another important characteristic is -- in
3 that metric or statistic is coined the effect
4 size. It essentially tells you how separated
5 cases and controls are from one another. Taking
6 into account the differences between the means
7 and the spread of the distributions.

8 So when -- if one were to look at this
9 characteristics, they will see that the effect
10 size was actually not changed. It was not
11 improved by the combination versus HIC1 alone,
12 which is the better marker. They are reported
13 increase in sensitivity, which was two-thirds of
14 CRCs; right? 65 percent was just 1 percent
15 point above the confidence -- 95 percent
16 confidence interval of the sensitivity of HIC1
17 alone.

18 So it was hardly a, you know, marginally
19 significant increase compared to that.

20 And the fact that the effect size was
21 essentially unchanged probably -- it means that
22 likely the effect would -- was not highly
23 significant. This is the first consideration
24 that I would make as a reader of this paper.

1 The second one was that they report numbers
2 for advanced adenomas. For advanced adenomas,
3 the overall performance of the test, again,
4 looking at sensitivity, specificity together,
5 and especially the area under the curve. The
6 performance was worse to a large extent because
7 of the drop in specificity.

8 So taken together, we see that the test
9 performs, at best, marginally better for
10 cancers. It may not even be bad at all. It
11 performs worse for advanced adenomas, which is
12 the critical endpoint that everybody is trying
13 to achieve.

14 And, in addition to that, if you remember,
15 the third criteria for what makes a test
16 promising is the utilization or uptake.

17 Here, you're combining FOBT, which is one
18 assay, with methylation, which is a very
19 different assay, which increase complexity of
20 the test.

21 So taking those three considerations
22 together, I would make a conclusion from this
23 data that HIC1 and FOBT is -- combining them
24 together is not the most promising approach.

1 I think that's exactly the argument they
2 make. That's the conclusion they make, and they
3 list -- in support of that, they list several
4 other potential methylation markers, like SFRP2.
5 They say it has very good sensitivity, not very
6 good specificity. But what they're saying is
7 there are others. Go look for other methylation
8 markers. Combine them together with HIC1, and
9 you hopefully are going to end up with a pretty
10 good prediction. I think that's -- that's what
11 I think this paper is about.

12 Based on -- and, like I said, I made this
13 conclusion based on my analysis of the data of
14 this paper, but also the conclusion that they
15 explicitly make.

16 Q So the conclusion they explicitly make is to add
17 additional sensitivity and specific methylation
18 markers to HIC1?

19 A Yeah.

20 Q It doesn't say: Add them but don't try --
21 include FOBT, does it?

22 A They don't. They don't say: Don't include
23 FOBT.

24 Q They also don't say anyplace in here that their

1 conclusion from the data is that the combination
2 of HIC1 and FOBT is worse than HIC1 alone, do
3 they?

4 MS. FERNANDS: Objection. Form.

5 THE DEPONENT: Right. So I think there is
6 a -- I think they don't explicitly, in their
7 conclusions, exclude FOBT. They don't talk
8 about it in words, but the only way I can
9 interpret their conclusion the way they wrote it
10 is that FOBT plus HIC1 is not promising.

11 And the reason I think it's pretty clear to
12 me that this is their conclusion as well, even
13 though they don't explicitly mention it -- they
14 don't have to mention it explicitly -- they
15 tested option A, which is FOBT plus HIC1. They
16 had all this data. They analyzed data. It's
17 their data. If they honestly believed that HIC1
18 plus FOBT is promising, they should have said
19 that, and they would have said that. They
20 explored A -- option A. They didn't think the
21 data showed that it's not promising. That's why
22 their conclusion is: We need to go route B,
23 find more -- you know, find a few more other
24 promising methylation markers and combine them.

1 We also want to -- I think we also need to
2 put ourselves back in when this paper was
3 written, which was 2005.

4 I remember the time -- and as I said
5 earlier, you know, during that time, this was a
6 time when everybody was interested in mutations
7 and cancer, which kind of made sense. They are
8 ideologically relevant. They create cancer.
9 Epigenetics was rapidly growing, so it was a new
10 kind of exciting thing to look at methylation
11 markers. That's what field was leaning
12 towards -- everybody was thinking.

13 So there was this consideration as well
14 that there must be other promising methylation
15 markers, or maybe, you know, nucleic acid
16 markers in general. That's real biology. Let's
17 combine those. There must be some -- some
18 really good markers out there. We need to
19 combine them.

20 Not to mention additional benefits of doing
21 that, that it's the same assay. You do
22 methylation, methylation. It's the same assay.
23 It simplifies the test. So there are clear
24 advantages of doing that.

1 I think that's why -- there are a
2 combination of all these reasons. They made
3 this conclusion.

4 BY MR. JONES:

5 Q You'll agree with me that in 2005, there were
6 FOBT assays commercially available; right?

7 A I believe so.

8 Q Will you agree with me that adding HIC1 to the
9 FOBT assay increased -- had a better -- sorry.
10 Scratch that.

11 Will you agree with me that the combined
12 HIC1 and FOBT assay had a better performance
13 than the FOBT assay alone?

14 A With that statement, I would disagree. The
15 question is what do we define as performance?
16 You used the word "performance."

17 If you talk about specifically sensitivity,
18 I would agree with that. The performance that
19 would include both sensitivity and specificity,
20 I don't see evidence of improvement here; in
21 fact, I see evidence of degradation of
22 performance for advanced adenomas.

23 Q The combined assay of HIC1 and FOBT detect
24 advanced adenomas at a higher sensitivity than

1 FOBT alone?

2 A It did detect -- that statement is correct, yes.
3 So the combination is better than FOBT alone;
4 however, that is not a correct comparison. The
5 correct comparison is always with a better
6 performing marker, which is HIC1. And what
7 we -- if you look at Table 2, I think this is
8 the -- I believe this is the advanced adenoma
9 detection table. They have patients with
10 advanced adenomas. They list HIC1 methylation,
11 FOBT. Right.

12 And if we look at this table, we see that
13 HIC1 detected four patients as cases. Correct.
14 So true positives.

15 FOBT detected one. But this one patient
16 was one of the patients that was also detected
17 by HIC1.

18 So adding FOBT to HIC1 did not improve
19 HIC1. And like I said, the comparison of a
20 combination should never be done with a worse
21 performing marker. That is not how it's done.
22 It's incorrect statistically. You always make
23 comparison with a better performing marker,
24 because if the combination performs as well as

1 the better performing marker even though -- it
2 performs better than -- okay. Scratch that.

3 So imagine combination -- a combination
4 performs better than the worst performing marker
5 but as good -- the same as the better performing
6 marker. Then a question is why wouldn't you
7 just stay with the marker that performs better.
8 You're not benefiting by adding the second
9 marker. And, in fact, there are a lot of
10 disadvantages with doing that. One of them is
11 increased complexity of the test. But the
12 second is if -- what they do here, if you
13 optimize the combination to increase
14 sensitivity, meaning that whenever any one of
15 them is positive, you call this a positive
16 combination; right? You almost invariably are
17 going to add false positives, which means it's
18 almost invariably going to drive specificity
19 down.

20 So that's why you always have to compare a
21 combination with a better performing marker.

22 In the field of biostatistics, the way,
23 kind of mathematically, to -- another way to
24 look at this mathematically is that if you have

1 two markers, one was them, we'll say, performs
2 better than the other -- let's say B is better
3 than A -- the performance, such as the
4 cumulative performance -- right -- combines
5 sensitivity and specificity -- AUC, ROC. All
6 the statistics are going to be dependent on the
7 distribution of the markers in cases -- among
8 cases and controls that can be captured by a
9 single statistic -- I mentioned before -- called
10 effect size -- coined the effect size.

11 Frequently, what we see is that when two
12 independent markers are combined, the effect
13 size is the arithmetic average of the two. So
14 you have well-performing marker versus a marker
15 that doesn't perform as well. You combine them
16 together, and your performance is going to be in
17 the middle.

18 Which means that it does not perform as
19 well as the better performing marker. In this
20 case, you're better off -- instead of combining
21 the two, you're better off staying with a single
22 marker that performs better, which is precisely
23 why in biomarker field, it's always -- the proof
24 of synergy is always on whoever proposes a

1 combination because, in so many cases, combining
2 markers actually leads to worse performance. In
3 fact, it's one of the well-known traps, so to
4 speak, for young investigators, who may think --
5 or inexperienced investigators, who might think
6 that combining different markers is always good;
7 in fact, in more cases than not, it actually
8 diminishes the performance.

9 So you always need to prove that it works
10 better. But you always compare it with the
11 better performing marker, which is HIC1 in this
12 case.

13 Q HIC1 wasn't a commercially used biomarker in
14 2005; right?

15 A Yeah. I think it was a research exploratory
16 biomarker. I don't think it was used
17 commercially.

18 Q FOBTs were a commercially used product in 2005?

19 A That is correct.

20 Q So adding HIC1 to the FOBT test was an
21 improvement in advanced adenoma detection over
22 the commercially available FOBT test at the
23 time; right?

24 MS. FERNANDS: Objection. Form.

1 THE DEPONENT: I would not say that because
2 that would contradict the way -- it would be
3 inconsistent with the way markers can be used.

4 In order for HIC1 to be used with FOBT, you
5 would have to commercialize and get approval for
6 HIC1 first. And at that point, you can, as
7 well, use it as a stand-alone marker.

8 BY MR. JONES:

9 Q So in the Cologuard clinical trial in Imperiale,
10 they compared the combined test to a FIT test;
11 right?

12 A Uh-huh.

13 Q So was the FIT test the better performing marker
14 than the DNA part of the Cologuard test?

15 A Well, I think --

16 MS. FERNANDS: Objection. Vague.

17 THE DEPONENT: I think we're comparing
18 apples and oranges here. So the -- in case of
19 Imperiale, two things happened, and these are
20 two independent things. First, you combine two
21 different markers. It happened to be FIT and
22 nucleic acid. It is this combination that led
23 to the high performance, the diagnostic
24 performance the test got. So let's call them A

1 and B. So what's important here is these are
2 two markers combined, right, and that forms
3 their test.

4 The comparison they're making is correctly
5 and properly so with a best comparator that is
6 commercially available, which is the FIT test.
7 The fact that FIT shows up twice as one of --
8 you know, as one of A and B that led to their
9 test, and a comparator, that is irrelevant.

10 So there are three tests here: A, nucleic
11 acid, or three types of biomarkers; right?
12 Biomarker A is nucleic acid.

13 Biomarker B is FIT.

14 And then there's a test, C, which also
15 happens to be FIT.

16 Even though FIT shows up in both
17 categories, that is irrelevant from my
18 perspective to this question.

19 So they combined FIT and nucleic acids
20 together to get the better test, but the
21 comparison was done with a commercially
22 available FIT. That is -- which is appropriate.

23 That is different for what's going on in
24 this paper and the hypothetical scenario that

1 you are describing. Because we can't just take
2 any biomarker -- let's say HIC1 -- and just add
3 it on top of FIT and say, You see, it performs
4 better than FIT.

5 In order for this to be in clinical
6 practice -- and that's what your question, I
7 understand, is referring to -- there has to be a
8 clinical trial, formal clinical trial. There
9 has to be FDA approval, summary regulatory
10 approval of some sort supported by clinical data
11 that HIC1 plus FOBT performs better than FOBT,
12 which means that HIC1 would have to be
13 clinically tested, developed in a way that can
14 be a robust test enough, and then validated and
15 regulatory approved. If you do all of this
16 work, and you have all this data on HIC1, and
17 you see that HIC1, as this data shows, in
18 combination with FOBT, does not give you any
19 advantage; in fact, actually, it gives you a
20 disadvantage compared to HIC1. At this point,
21 you just run clinically and hope for HIC1 alone.

22 So there's a very different -- these are
23 very different scenarios.

24 \\

1 BY MR. JONES:

2 Q You'll agree with me that if you tested with
3 HIC1 alone, there would be patients with
4 colorectal cancer that were not detected that
5 would be detected if you tested with HIC1 and
6 FOBT together?

7 A I agree with that, yes. The combination of --

8 Q And you'll agree with me that those patients who
9 were not tested for HIC1 with -- in the
10 combination, were tested for HIC1 alone and were
11 missed because of that, those patients would
12 have likely a worse outcome than if they were
13 tested together; right?

14 MS. FERNANDS: Objection. Form.

15 THE DEPONENT: I agree with that. I think
16 the data does show that the combination of HIC1
17 plus FOBT is -- has a sort of probability of
18 detecting more colorectal cancers than HIC1 or
19 FOBT alone, but it's very important to qualify
20 the statement, considering two very critical
21 caveats. One of them is that -- is statistical
22 significance.

23 So the question is this increase in
24 sensitivity. Two-thirds of CRC is detected by

1 the combination. Is that statistically
2 significant? There's a difference between
3 substantially higher and significantly higher.

4 And I don't think this data provides
5 adequate proof of statistical significance of
6 the result. Maybe it is. Maybe they need to
7 recruit more patients in order to say that. But
8 this data is -- does not really get us there
9 because a -- the 65 percent sensitivity is just
10 one single percent point above the 95 percent
11 confidence interval of sensitivity for HIC
12 alone. And if we look at the confidence
13 intervals of the combination -- sensitivity of
14 the combination versus sensitivity of HIC alone,
15 the 95 percent confidence intervals actually
16 significantly overlap. That's the first thing.

17 The second reason is if you -- one were to
18 look at the effect size over the combination
19 versus HIC1, we would see that they are almost
20 indistinguishable. So there is really not a lot
21 of -- it's not a very strong proof -- it is not
22 a strong proof here. There is not clear
23 indication here that the combination actually
24 does perform better in sensitivity than HIC1

1 alone.

2 And then -- and we can never, ever look at
3 sensitivity as a single measure. Just like we
4 can never ever look at specificity as a single
5 measure, or uptake as a single measure.

6 We also have to always look at these two
7 things in combination. If we're talking about
8 diagnostic performance, you have to look at
9 sensitivity, specificity. And specificity, we
10 see in this data, even for colorectal cancers,
11 it's -- there is a significant drop in
12 specificity.

13 There is a -- I understand the statement
14 they're making, that there are -- two-thirds of
15 CRCs have been picked up, but I can give you a
16 task that picks up every single CRC in the
17 country. We name every patient positive for
18 cancer, and that's a test that gives you
19 100 percent sensitivity.

20 Obviously, nobody in their right mind would
21 propose a test like that because it would have
22 terrible specificity. It's an extreme -- it's
23 an extreme case, of course. But it's an example
24 why is that -- I don't think any expert would

1 look at -- any person in the field would look at
2 sensitivity alone.

3 BY MR. JONES:

4 Q In this case, the specificity for the combined
5 test was 89 percent; right?

6 A I can check the exact number. It sounds about
7 right.

8 Q And that's higher than the specificity for
9 colorectal cancer for Cologuard; right?

10 A It is. It is, right. So the specificity of --
11 let me just check the number and make sure I got
12 it right. So the specificity of Cologuard is --
13 depending on which population you compare -- you
14 look at -- the most, you know, comparable
15 population here is patients with negative
16 results in colonoscopy. So their Cologuard's
17 specificity was 89.8 percent.

18 So 89. So we compare 89.8 percent with --
19 let me just get an exact number here of the
20 combination. I think it says -- let's see.

21 Q Just to make things easier, in paragraph 64 of
22 your declaration, you give sensitivity and
23 specificity.

24 A Thank you.

1 Based on -- the data in Lehnard also show
2 that sensitivity and specificity of HIC1 alone
3 for cancers are 44 and 98 percent respectively.
4 And below that, if this particular combination
5 is optimized for sensitivity, the result is that
6 sensitivity, specificity for cancers of the
7 combination are 65 and 89 percent. So the
8 specificity of Cologuard is 89.8 percent.

9 So, actually, based on this number, it is
10 .8 percent higher, which I wouldn't call
11 significant. It's about the same.

12 Q About the same?

13 A About the same.

14 MR. JONES: We can take a break for lunch.

15 (Break.)

16 (Exhibit No. 1005 marked.)

17 BY MR. JONES:

18 Q This is another document. So I've handed you
19 Exhibit 1005.

20 Do you recognize this as a paper by Vilkin,
21 et al., entitled "Performance, Characteristics,
22 and Evaluation of an Automated, Developed, and
23 Quantitative Immunochemical Fecal Occult Blood
24 Screening Test"?

1 A I do.

2 Q Can you look at paragraph 69 of your
3 declaration?

4 A I am there.

5 Q And this is the Vilkin paper -- Exhibit 1005 is
6 the Vilkin paper that you discuss in the section
7 starting paragraph 69; right?

8 A I see that, yes.

9 Q If you turn your attention back to Vilkin, and
10 specifically the start of the paper, which it
11 looks like you're looking at. Under the
12 Objectives section of the abstract, Vilkin
13 states that guaiac fecal occult -- sorry.
14 Guaiac fecal occult colorectal cancer -- it's
15 after lunch.

16 Let me start reading that again.

17 It's says, "Guaiac fecal occult blood
18 colorectal cancer screening tests, FOBT, are
19 faulted for low sensitivity and non-specificity
20 for human hemoglobin HB."

21 Do you see that?

22 A I see that.

23 Q You'll agree with me that here Vilkin is
24 discussing one of the disadvantages of gFOBT

1 tests; right?

2 A Right.

3 Q In the next sentence, Vilkin states, "Automated
4 developed immunochemical human HB, FOBT, or
5 iFOBT is specific, eliminates diet restrictions,
6 and hemoglobin quantification; allows selection
7 of a threshold for colonoscopy."

8 Do you see that?

9 A Yes.

10 Q Here, Vilkin is teaching advantages of
11 quantitative immunochemical FOBT tests; right?

12 A Correct.

13 Q And Vilkin calls these tests iFOBT tests?

14 A Yes.

15 Q And will you agree with me that other places
16 call these tests FIT tests?

17 A Correct.

18 Q F-I-T test; right?

19 A F-I-T, yes.

20 Q And you'll agree that iFOBT and FIT are two
21 acronyms that mean the same thing?

22 A I do.

23 Q And if you look at the body of the paper, the --
24 I guess it would be the introductory section

1 below the abstract.

2 The first sentence says, "The standard
3 guaiac fecal occult blood test, gFOBT, is
4 faulted for its low sensitivity for a
5 significant colorectal cancer neoplasia,
6 colorectal cancer, and advanced adenomas polyps.
7 Low specificity due to non-specificity for human
8 hemoglobin."

9 Do you see that?

10 A I see that.

11 Q Where it refers to non-specificity for human
12 hemoglobin, this is a reference to the fact that
13 gFOBT assays can also detect animal hemoglobin;
14 right?

15 A Correct. Yes.

16 Q And that includes animal hemoglobin that is
17 found in food?

18 A Yes.

19 Q That's why gFOBT tests typically require dietary
20 restriction before being used?

21 A Yes.

22 Q And you'll agree with me that the dietary
23 restriction associated with gFOBT tests is a
24 disadvantage of gFOBT tests; right?

1 A I agree.

2 Q And you'll agree with me that dietary
3 restriction is typically not a requirement of
4 FIT tests?

5 A I do. I agree.

6 Q If you look at the paragraph on the top, right
7 column of this paper, it says, "The automated,
8 developed, and quantitated iFOBT is human HB
9 specific" -- that's hemoglobin specific --
10 "eliminates the need for diet restrictions, and
11 the hemoglobin quantification allows selection
12 of a suitable threshold level for follow-up
13 colonoscopy."

14 Right?

15 A Yes. I see that.

16 Q Once again, Vilkin's listing advantages of FIT
17 assays is like the one disclosed in this paper;
18 right?

19 MS. FERNANDS: Objection. Form.

20 THE DEPONENT: Could you repeat the
21 question?

22 BY MR. JONES:

23 Q In this sentence, in the top of the right-hand
24 column, Vilkin is providing advantages of

1 automated, developed, and quantitated iFOBT
2 assays, like the ones described in this paper,
3 over gFOBT assays; right?

4 A I agree with that, yes.

5 Q Going back to the left-hand column. Last
6 sentence of the first paragraph. This sentence
7 Vilkin says that, "gFOBT assays are also faulted
8 by the possibility of inaccurate development in
9 evaluation by inadequately trained personnel."

10 Do you see that?

11 A Let me just make sure I got this right.

12 Right. That's correct.

13 Q Do you agree with me that Vilkin is suggesting
14 that it would be advantageous to have
15 professional laboratory personnel perform FOBT
16 assays?

17 MS. FERNANDS: Objection. Form.

18 THE DEPONENT: Are you asking if they're
19 suggesting that it's better for FOBT to be
20 performed by a professional lab versus --

21 BY MR. JONES:

22 Q Than a subject at home.

23 Let me clarify the question.

24 This sentence refers to inaccurate

1 development and evaluation of inadequately
2 trained personnel; right?

3 A Right.

4 Q Would you agree with me that there's an
5 advantage to having professional laboratory
6 personnel do the development and evaluation of
7 FOBT tests?

8 MS. FERNANDS: Objection to form.

9 THE DEPONENT: Well, generally there's an
10 advantage of well-trained personnel in the
11 professional labs to perform a test for sure.

12 I think what Vilkin does here is, in the
13 first paragraph, explains what perceived
14 disadvantages of FOBT -- gFOBT are. And I agree
15 with what's listed: Dietary restrictions, low
16 sensitivity.

17 The fact that it's typically a patient who
18 has to, for example, smear the stool on the
19 slide, which is not necessarily highly
20 desirable, and increases the complexity of the
21 test as well, these are the things that they
22 discuss.

23 There's limitations of gFOBT as practiced
24 at the time when Vilkin's paper was written. I

1 don't think in this paragraph they say that FIT
2 addresses all of these problems -- in the first
3 paragraph.

4 BY MR. JONES:

5 Q Okay. Would you agree that in the following
6 paragraph, Vilkin -- sorry, I should say in the
7 following paragraphs, the following two
8 paragraphs, Vilkin discusses how the automated
9 FIT assay addresses the problems he sets forth
10 in the first paragraph?

11 A Right. I think Vilkin does say that iFOBT
12 addresses some of the problems listed above. In
13 particular, they mention the fact that iFOBT is
14 quantitative, so you can choose different
15 thresholds, which would not be possible with
16 gFOBT.

17 They don't -- they address some of the
18 limitations. They don't address all of them,
19 but that's the intent of this paragraph, as far
20 as I understand.

21 Q If you turn to the following page, you'll see
22 there's a section called "Fecal Sampling."

23 A Yes.

24 Q And this refers to figure 1.

1 Do you see that, this section?

2 A Yeah.

3 Q You'll agree with me that the left-hand panel of
4 figure 1 is a depiction of the fecal sampling --
5 sorry -- what they call the fecal test sampling
6 device used in the Vilkin assay?

7 A Right. The stool probe in the storage tube.
8 Yes, I see it.

9 Q Will you agree with me that when the device of
10 Vilkin is used, a portion of the fecal sample is
11 removed and put in a sealable container?

12 MS. FERNANDS: Objection. Form.

13 THE DEPONENT: Based on this paper, so
14 Vilkin is -- in Vilkin's iFOBT, part of the
15 procedure is after the defecation happens; part
16 of the stool sample is removed using a probe and
17 put in a container.

18 BY MR. JONES:

19 Q And that container is sealed; right?

20 A I believe so. Especially in their case because
21 they do three collections, and they need to keep
22 their samples in the fridge.

23 So I think for them, it was particularly
24 helpful to have a sealed container because of

1 the contamination issues while the samples were
2 placed in the fridge.

3 Q A sealed container would be useful any time
4 you're shipping the sample to a laboratory;
5 right?

6 A For sure, yeah.

7 Q And the sealed container contains heme
8 stabilizing buffer?

9 A I believe so.

10 Q Then once the sealed container is sealed,
11 they're then sent to the developing laboratory?

12 MS. FERNANDS: Objection. Form.

13 THE DEPONENT: Is your question whether
14 after the sample is collected and put in a
15 container, then the samples are sent to a
16 laboratory?

17 Yes, they are sent to the laboratory.

18 BY MR. JONES:

19 Q Then in the laboratory, you'll agree with me
20 that the fecal samples is tested for an amount
21 of hemoglobin in that fecal portion?

22 A Yes.

23 Q I pointed out the last sentence of this fecal
24 sampling paragraph. It says, "Samples are

1 double-closed in Ziplock bags and kept in a
2 refrigerator until they are returned to the
3 sampling laboratory, where they're also kept at
4 4 degrees until development."

5 Right?

6 MS. FERNANDS: Objection. Form.

7 BY MR. JONES:

8 Q Did I misread that?

9 MS. FERNANDS: A little bit.

10 BY MR. JONES:

11 Q Let me re-read that.

12 The last sentence says, "Samples are
13 double-closed in Ziploc bags and kept in the
14 refrigerator until returned to the developing
15 laboratory, where they are also kept at
16 4 degrees Celcius until development."

17 A Right. That's what it says.

18 Q Will you agree with me that if a sample were
19 sent to the developing laboratory immediately
20 after it was collected, it would not need to be
21 refrigerated in the patient's home?

22 MS. FERNANDS: Objection. Form.

23 THE DEPONENT: I don't think this paper
24 provides enough data to suggest -- to test the

1 statement, whether it's -- it will be required
2 or not if the samples were not kept for three
3 days.

4 It might be the case or might not be. I
5 just can't really evaluate that.

6 And part of the reason is that I cannot
7 rule out, based on the data in this paper, I
8 cannot rule out a possibility that the
9 refrigeration of fresh samples performs certain
10 chemical function on the samples that actually
11 allows better detection. For example, there's
12 complex samples. Certain enzymes might be
13 active upon fresh collection. These enzymes
14 have certain degradation time as well.
15 Refrigerating the sample may slow down the
16 activity of this enzyme. It might negatively
17 affect the sample.

18 I'm not saying that that's what would
19 happen to the samples. All I'm saying is that
20 this was not tested in this paper.

21 So I cannot really say whether what you
22 said is correct or not. Refrigeration might
23 have been an absolutely essential step, or it
24 might not have been, regardless of how many

1 samples they were collecting.

2 It's something that could have been
3 investigated, but they should have done, then, a
4 separate study. They have splitting patients
5 collecting some patients -- patient samples
6 without refrigeration, and doing the same
7 analysis, comparing their markers.

8 In the field, it's fairly well-known that
9 little things like that -- refrigeration,
10 temperature, refrigeration, freezes or not --
11 they might result in significantly different
12 results, precisely because these are complex
13 samples from a living organism.

14 BY MR. JONES:

15 Q Are you aware of any examples where immediate
16 refrigeration has been shown to have an effect
17 on a FIT test?

18 A No. I can't give examples related to FIT test.

19 Q The sentence --

20 A I don't think it was very well investigated.

21 Q Sorry. Sorry. I interrupted.

22 This sentence doesn't give the conditions
23 under which the fecal samples were shipped to
24 the lab, does it?

1 A I don't think so. I didn't find any.

2 Q Can you go to page 2524?

3 A All right.

4 Q If you look at the last full paragraph in the
5 left column?

6 A The one that starts, "At present?"

7 Q Yes.

8 A Okay.

9 Q It says, "At present, we will continue with
10 collecting three annual fecal tests. As we have
11 confirmed the additive clinical value of
12 repeated occult blood testing in this high risk
13 population."

14 Do you see that?

15 A Yes.

16 Q Here, the authors are talking about continuing
17 to do three FIT tests over the course of a year;
18 right?

19 A Yes.

20 Q Not three FIT tests over the course of three
21 days; right?

22 A I believe so. They say "three annual." So I
23 presume this is three per year.

24 Q And the authors are saying that this is what

1 they're going to continue to do in a high-risk
2 population; right?

3 A Correct. Their study population is high risk in
4 this paper.

5 Q Would you agree with me that often colorectal
6 cancer testing frequency is more frequent in
7 high risk populations than in normal
8 populations?

9 MS. FERNANDS: Objection. Form.

10 THE DEPONENT: I don't have data in front
11 of me to argue one way or another. Ideally,
12 what investigators in the field have been trying
13 to come up is a test that can be used in
14 asymptomatic population across all eligible
15 population.

16 So this paper deals specifically with a
17 high risk, but I don't have statistics in front
18 of me to address the question whether
19 historically FOBTs have been used predominantly
20 in high-risk patients.

21 That clearly was not the intent. The
22 intent was to have a test that would work for
23 everybody. But in order to me -- for me to
24 address the question, I'll have to look actually

1 at statistics of how it has been used.

2 BY MR. JONES:

3 Q So, first, I just wanted to clarify one word in
4 your last answer. You said, "Ideally, what
5 investigators in the fields have been trying to
6 come up with is a test that can be used in the"
7 --

8 A In general population.

9 Q Okay. So it was recorded as in "symptomatic"
10 population?

11 A Asymptomatic.

12 Q That's how I heard it. It was wrong on the
13 transcript.

14 Okay. Will you agree with me that even in
15 a broader sense, it's often the case that
16 high-risk populations are recommended to be
17 tested more frequently for cancer than normal
18 risk populations?

19 A That is correct. And, in particular, high-risk
20 patients are typically recommended to receive
21 more frequent colonoscopies. Of course, you
22 really don't want to miss significant lesions in
23 these patients, but most doctors at this point
24 recommend a colonoscopy in high-risk patients.

1 Q The next sentence in this paragraph, the authors
2 write, "This is in contrast to the annual
3 two-day average risk population iFOBT collection
4 as routinely used in Japan, United States, and
5 Australia, and one-day, bi-annual testing as
6 performed in Italy."

7 Do you see that?

8 A Yeah, I see that.

9 Q So this looks like -- would you agree with me
10 that different countries -- at least Japan,
11 United States, Australia -- have a different
12 frequency of testing than Italy, according to
13 this sentence?

14 MS. FERNANDS: Objection. Form.

15 THE DEPONENT: I would say so, based on the
16 sentences.

17 BY MR. JONES:

18 Q You'll agree with me a one-day, bi-annual
19 testing performed in Italy would be one FIT test
20 every other year; right?

21 A Well, I believe the word "bi-annual" may mean
22 either twice a year or once every two years --
23 depending on the context. I agree with you. I
24 think in this case, most likely my

1 interpretation would be one every three years.

2 But the word "bi-annual" is actually
3 confusing.

4 Q I'll represent to you I Googled bi-annual
5 spelled that way, and at least google told me
6 that it was once every two years, which seems to
7 be consistent with what you think is the most
8 likely.

9 A I think that's what the context says.

10 Q But I agree. I had to look it up to make sure.

11 And then the next paragraph says -- it
12 starts with, "The decision on the number of
13 fecal samples to be obtained in the optimal
14 fecal hemoglobin threshold chosen for screening,
15 an average risk population will also involve an
16 evaluation of cost benefit."

17 Do you see that?

18 A I see that.

19 Q So you'll agree with me that Vilkin is saying
20 that the number of fecal samples to be used in
21 the test and the optimal hemoglobin thresholds
22 to test for should be decided based on a
23 cost-benefit analysis?

24 MS. FERNANDS: Objection. Form.

1 THE DEPONENT: I do agree that a
2 cost-benefit analysis would be a significant
3 consideration in -- in this particular case, how
4 many tests per year realistically you want to
5 administer for sure.

6 I wouldn't say it's the only consideration,
7 but it is one of the important considerations.

8 BY MR. JONES:

9 Q So you'll agree with me that Vilkin is not
10 saying that you should always collect three
11 samples on three consecutive days for all
12 populations when running this test; right?

13 MS. FERNANDS: Objection. Form.

14 THE DEPONENT: I'm not sure I -- I'm not
15 sure I understood the question correctly.

16 Would you mind repeating it?

17 BY MR. JONES:

18 Q So in the sentence, Vilkin is saying that the
19 number of fecal samples that should be obtained
20 and the threshold used should be evaluated and
21 determined by a cost-benefit analysis; right?

22 A I think what they're saying is that there's a
23 question, "How many samples per year you want to
24 collect?"

1 And, in part, it can be -- one of the
2 considerations is going to be cost benefit. In
3 the context that other considerations are going
4 to involve how much benefit you're getting, if
5 any at all, in regards to sensitivity and
6 specificity. And that's part of their study
7 they are doing.

8 Q So what I'm saying is -- or what I'm asking is
9 Vilkin is not saying that all populations should
10 necessarily use the FIT test describes -- sorry.

11 Let me start -- scratch that and let me
12 start over.

13 So Vilkin is not saying that for all
14 populations, you necessarily have to collect
15 three fecal samples on three consecutive days
16 when this assay is used in clinical practice;
17 right?

18 A Three consecutive days versus three per year, or
19 three consecutive days versus one day a year.
20 Which comparison are you referring to?

21 Q I'm not actually referring to a specific
22 comparison, because you'll agree with me that
23 Vilkin is saying that there's an evaluation that
24 would be required in order to determine whether

1 you would want to do, for example, one a year or
2 two a year or three a year or one every other
3 year in a given population; right?

4 A Correct. Yes.

5 Q So my question was just: Vilkin isn't saying
6 that the answer to that is necessarily three
7 consecutive days of sampling for testing? It
8 could be some other frequency; right?

9 MS. FERNANDS: Objection. Form.

10 THE DEPONENT: Well, I think, based on the
11 data that they have in this paper, based on the
12 study they did, their conclusion is that three
13 is an optimal number because collecting one or
14 two does not give you good enough, from their
15 perspective, sensitivity and specificity.
16 Collecting three samples, it results in what
17 they show very high sensitivity and specificity
18 so that collecting four samples would be, well,
19 an overkill. Their sensitivity and specificity
20 for three samples are really excellent.

21 The sensitivity for CRCs is 100 percent.
22 Specificity is -- I think it is also very high.
23 I'm trying to find the number. I think it was,
24 like, mid-90th percentile. And for cancers,

1 possibly advanced adenomas, it's over 76 percent
2 sensitivity and the same specificity.

3 So adding an additional few samples would,
4 at best, have marginal -- if at all -- effect on
5 the performance with significantly added costs
6 and complexity for patients.

7 That's why -- what they say here is, Well,
8 we'll continue with collecting three annual
9 fecal tests. So that is their decision, based
10 on their data: Three is the optimal number.
11 And what they go ahead and say is that this
12 number is different from what is currently done
13 in other countries.

14 Having said that, the regimen for FOBT
15 screen in other countries -- Japan,
16 United States, Italy -- that they quote does not
17 include the hindsight of the data that they
18 provide in this paper.

19 So their conclusion is three is a good
20 number. We'll continue doing that. We think
21 it's -- we think it's the right number.

22 BY MR. JONES:

23 Q They specifically say that three is the
24 number -- three annual samples is what they're

1 going to continue to do in the high-risk
2 population; right?

3 A Right. Yes.

4 Q And that's not three consecutive days. It's
5 three over the course of a year?

6 A Right. That's my understanding, too, that
7 they -- even though in their study they did
8 three consecutive collections, what they say in
9 this paragraph, that they believe, at least,
10 that they can do three annual.

11 Q So that's the reference to high-risk population
12 in that sentence.

13 If you look at the first sentence in the
14 next paragraph where it's talking about the
15 decision of the number of fecal samples --

16 A Uh-huh.

17 Q -- this is a reference to using cost-benefit
18 analysis to see what the right number is for an
19 average risk population; right?

20 A That's correct. And I think the key word here
21 is "also;" right? What they say is that the
22 hemoglobin threshold chosen, which is one of the
23 aspects, what they studied, and the number of
24 fecal samples for average risk population would

1 also involve an evaluation of cost benefit.

2 So "also" refers to what they did with the
3 high risk. What they're saying is that their
4 study population is high risk. They came up
5 with their assessment as three is the right
6 number. So when anybody else thinks about what
7 to do with average risk, they would have to
8 repeat -- do a study similar to what they did
9 here, and that is their -- the part of the
10 cost-benefit analysis.

11 And others can arrive at a number, which
12 might be three. It might be -- it might be a
13 different number. They cannot really make this
14 conclusion because they did not study average
15 risk population in this paper.

16 So "also" is the key word. They're saying
17 repeat the study or do a similar study, and then
18 make a decision in a way similar to what we did
19 for the high-risk population.

20 (Exhibit No. 1006 marked.)

21 BY MR. JONES:

22 Q I'll hand you another paper. It should be
23 familiar, I think. If you want, you can turn to
24 page 35 of your declaration, starting at

1 paragraph 74. I'm going to ask you questions
2 about this paper.

3 So I put before you Exhibit 1006.

4 Do you recognize this as a paper by
5 Itzkowitz, et al, titled: "Improved Fecal DNA
6 Test for Colorectal Cancer Screening"?

7 A I do, yeah. I see it.

8 Q And this is the paper you refer to in the
9 section of your declaration, starting in
10 paragraph 74?

11 A Correct.

12 Q Do you recognize that this is a paper that was
13 co-authored by people employed by Exact
14 Sciences?

15 A I do recognize a few names, yes. I believe they
16 work at Exact Sciences. Again, I can't really
17 talk about -- I can't really talk about every
18 one of the co-authors, but I recognize some of
19 the names.

20 Q In the Author Affiliation section, right under
21 the authors, there's the double asterisks that
22 identify authors who are affiliated with Exact
23 Sciences?

24 A Right. Yeah.

1 Q Back when they were in Marlborough,
2 Massachusetts?

3 A Uh-huh.

4 Q If you look at page 112 of this paper, there's a
5 section titled "Sample Collection."

6 A Uh-huh. Yes, I see that.

7 Q Will you agree with me that when the -- when the
8 assay described in Itzkowitz is performed, a
9 fecal sample is collected at home by a patient
10 by direct defecation into a sealable collection
11 vessel?

12 A Let me just make sure I'm on the right sentence
13 here.

14 Right.

15 Q So the answer is "yes"?

16 A Yes.

17 Q Okay. So after direct defecation into the stool
18 collection kit, the fecal sample is combined
19 with a DNA stabilizing buffer; right?

20 A Right. Yes.

21 Q The sample is shipped to a diagnostic
22 laboratory?

23 A Yes.

24 Q And would it be fair to assume that the

1 container is sealed before it is shipped to the
2 diagnostic laboratory?

3 A Right. Even though I don't think they
4 specifically say "sealed," but I think it's a
5 fairly good assumption.

6 Q And at the diagnostic laboratory, DNA is
7 extracted from the fecal sample?

8 A I'm sorry. Could you repeat that? I still have
9 the visual picture of unsealed container.

10 Q So they perform different DNA assays on the
11 fecal sample at the diagnostic laboratory;
12 right?

13 A Yes, they did. Yeah.

14 Q Will you agree with me that before performing
15 those assays, DNA is extracted from the fecal
16 sample?

17 A Yes.

18 Q And then at the laboratory, the extracted DNA is
19 subjected to one or more tests; right?

20 A Yes. They determined some of the nucleic acid
21 markers for a DNA sample.

22 Q So, for example, in some versions of the assay,
23 the extracted DNA is tested for an amount of
24 methylated vimentin DNA?

1 A Yes.

2 Q Would you agree with me that the stool
3 collection process of Itzkowitz requires less
4 fecal manipulation by the patient than
5 Cologuard?

6 MS. FERNANDS: Objection. Form.

7 THE DEPONENT: I think it does.

8 BY MR. JONES:

9 Q If you go to page 116.

10 A All right.

11 Q In the first full paragraph of this -- of the
12 left-hand column, in the second sentence, it
13 says, Our finding build upon the promising
14 results of the prototype, version one
15 multi-target DNA panel, that showed 52 percent
16 sensitivity and 94 percent specificity for
17 colorectal cancer in asymptomatic average risk
18 individuals.

19 Do you see that?

20 A So this is the sentence with the 52 percent to
21 72.5 percent; right? Is that the sentence?

22 Q I actually read the -- a sentence before that
23 where it talked about version one where it
24 said --

1 A Oh, I see.

2 Q -- that version one showed 52 percent
3 sensitivity and 94 percent specificity.

4 A Right. I see that.

5 Q And then by using improved methods for
6 stabilizing DNA during specimen transport,
7 better extraction of DNA from stool, they find
8 that the sensitivity of the version one marker
9 panel is increased from 52 percent to 72.5
10 percent; right?

11 A Right. Correct.

12 Q And if you look a couple sentences down, the
13 sentence starts with, "This increase."

14 So it says, "This increase in sensitivity
15 for the full version one panel was achieved at
16 the expense of a relatively minor decrease in
17 specificity from 94.4 percent to 89.3 percent."

18 Do you see that?

19 A Right. I see that.

20 Q So in this paragraph, Itzkowitz is reporting
21 that by using improved methods for stabilizing
22 DNA during transport, better extraction of DNA,
23 they're able to create an improved assay that
24 had more than 20 percent increase in sensitivity

1 at the cost of only a small -- relatively
2 small -- well, 5 percent decrease in
3 specificity; right?

4 A Correct.

5 Q If you go to the abstract, under the Results
6 section, first -- the first sentence refers to
7 what we were just talking about, which is by
8 using the optimally preserved and purified --
9 sorry -- by using DNA that was optimally
10 preserved and purified from stool, the
11 sensitivity of the prototype version one assay
12 increased to 72.5 percent because of the
13 enhanced performance of DIA.

14 Do you see that?

15 A Yes, I see that.

16 Q And then for version two of the assay, they look
17 at vimentin gene methylation in that assay;
18 right?

19 A Right.

20 Q And they say, "Vimentin gene methylation alone
21 provided sensitivity and specificity of
22 72.5 percent and 86.9 percent," respectively;
23 right?

24 A Correct.

1 Q And then when they say the optimal combination
2 of vimentin methylation plus DIA resulted in
3 87.5 percent sensitivity and 82 percent
4 specificity; right?

5 A Correct. Yes.

6 Q So when they further improve the assay by using
7 the vimentin methylation, they increased the
8 sensitivity by about 13 percent, but at the cost
9 of further decreasing the specificity down to
10 82 percent; right?

11 A Right.

12 Q So here, once again, Exact is improving an assay
13 by increasing sensitivity at some cost to
14 specificity; right?

15 A They do. But, again, I think what you said
16 needs to be somewhat qualified.

17 I think there are two things -- there are
18 two separate statements they're making in this
19 results and conclusion. So the first one is
20 what you said, they are improving other assays,
21 and they see a significant increase in
22 sensitivity and a small drop in specificity.

23 Looking at their statistics, at their
24 confidence intervals, they seem -- it seems to

1 be a statistically significant result because it
2 is outside of the 95 -- the improvement is
3 outside of the 95 percent confidence interval.

4 I think that's why they're able to make
5 this conclusion.

6 This is the first part.

7 The second part -- and I want to make sure
8 we're not lumping them together -- is they are
9 looking at a little different assay, just
10 different biomarker, vimentin, in combination
11 with DIA, and they're saying that there is --
12 they say the same sensitivity for vimentin alone
13 or higher sensitivity for the combination of
14 these two biomarkers with a small drop in
15 specificity.

16 The essence of what they're comparing here
17 is not just goes well beyond -- this is very
18 important. It goes beyond just comparing
19 sensitivity and specificity. This is a
20 comparison they're making between an assay that
21 employs a large number of potential biomarkers
22 and a prediction rule, based on just two
23 biomarkers, vimentin and DIA.

24 And for them, just like for people who work

1 in the field, that would be a very important
2 comparison. Why? Because the fewer biomarkers
3 or potential biomarker candidates you combine in
4 the prediction rule, the less likely you are to
5 overfit the data during the prediction rule
6 development or initial validation. The more
7 likely it is the data -- the performance
8 characteristics -- sensitivity, specificity --
9 will be confirmed in a larger study.

10 When one combines multiple markers, a lot
11 of markers together, there is just a higher
12 chance of over-fitting the prediction rule and
13 then end up with a failed validation.

14 So in this context, most practitioners in
15 the field would prefer to have as few markers
16 together as possible, even at certain expense of
17 a drop in some of the performance
18 characteristics. And that's the comparison
19 they're making. Look, we look at only two
20 biomarkers, and they still perform quite well.
21 So it's not so much about whether there is a
22 significant trade-off between sensitivity and
23 specificities. It's more about the fact that
24 they actually performed quite competitively

1 compared to the version one that employed more
2 markers. So somewhat two different comparisons
3 they're making here.

4 Q So the original prototype version one of the
5 assay had a specificity of 94 percent in average
6 risk individuals; right?

7 A Let me just make sure. 94, yes. 94, yeah.
8 94.4.

9 Q And the final assay they arrived at had a
10 specificity of 82 percent; right?

11 A Correct. Yeah. But the assay two had two
12 significant advantages; one of them is
13 considerably higher, and statistically a higher
14 sensitivity. But the second important aspect is
15 that the second version just had two biomarkers
16 as opposed to a lot. And that is -- that is
17 very important.

18 Q So that first advantage that you -- the first
19 significant advantage that you mentioned was a
20 statistically higher sensitivity. That's a
21 statistically higher sensitivity for colorectal
22 cancer; right?

23 MS. FERNANDS: Objection. Form.

24 THE DEPONENT: Correct.

1 BY MR. JONES:

2 Q Because in Itzkowitz, Exact doesn't report any
3 results regarding the sensitivity of their
4 assays for advanced adenoma, does it?

5 A Can you repeat the question?

6 Q In this Itzkowitz paper, Exact doesn't report
7 any results regarding the sensitivity of any of
8 these tests for advanced adenoma, does it?

9 A They did not test it on advanced adenoma
10 patients, correct.

11 Q So if you look at paragraph 76 of your
12 declaration, about two-thirds of the way of the
13 paragraph, you have a quote from Itzkowitz that
14 says, "These findings support results from the
15 previous multi-center study, which subjects
16 preferred fecal DNA testing to both fecal occult
17 blood test and colonoscopy."

18 Do you see that?

19 A I see that, yes.

20 Q And in support of that, Itzkowitz cites to a
21 paper by Schroy?

22 A Yes.

23 Q Did you review Schroy?

24 A I did review Schroy.

1 Q And if you go to paragraph 112 of your
2 declaration.

3 A Which paragraph are we looking at?

4 Q 112.

5 A Right.

6 Q And here, once again -- sorry. Scratch that.

7 Here you say "Itzkowitz recognized
8 well-known need for patient acceptability."

9 Right? Paragraph 112?

10 A "Inherent in the success of any screen test is
11 patient acceptance."

12 Right? Is that the sentence?

13 Q Well, I read the sentence before, but it's okay.
14 It's the same.

15 I said -- the sentence before, you say,
16 "Itzkowitz recognized the well-known need for
17 patient acceptability."

18 A Yes.

19 Q Then you say -- Itzkowitz states, "Inherent in
20 excess of any screening test is patient
21 acceptance. Our preliminary experience with the
22 new fecal DNA test, which patients add
23 stabilization buffer to stool, confirms a very
24 high degree of patient satisfaction."

1 Do you see that?

2 A I see that, yes.

3 Q And you, again, quote Itzkowitz and say,
4 "Itzkowitz observed that."

5 Its findings are supported by the previous
6 multi-center study in which subjects preferred
7 fecal DNA testing to both fecal occult blood
8 test and colonoscopy.

9 Do you see that?

10 MS. FERNANDS: Objection. Form.

11 BY MR. JONES:

12 Q Okay. I'm going to read that again.

13 You say, "Itzkowitz observed that its
14 findings support results from the previous
15 multicenter study in which subjects preferred
16 fecal DNA testing to both the fecal occult blood
17 test and colonoscopy."

18 Do you see that?

19 A I see that, yes.

20 (Exhibit No. 2048 marked.)

21 BY MR. JONES:

22 Q I'm putting before you Exhibit 2048.

23 MS. FERNANDS: Multiple copies came to this
24 side, for the witness as well.

1 MR. JONES: Okay. Everyone has a copy.

2 MS. FERNANDS: We all have a copy.

3 BY MR. JONES:

4 Q I put before you Exhibit 2048, and do you
5 recognize this as the Schroy paper that's cited
6 in Itzkowitz?

7 A I do.

8 Q And you said you considered this paper when you
9 were drafting your declaration; right?

10 A Yes. Yes, I did.

11 Q If you go to the very last page, I guess the
12 second to the last page, so it's page 6 of 7 of
13 the document. At the very end, you'll see the
14 work on this paper was supported by Exact
15 Sciences?

16 A I see that, yes.

17 Q If you go to the second page of this document,
18 page 2 of 7, under Study Design -- actually,
19 before I get into that. You'll agree with me
20 that this paper looks at patient perception of a
21 DNA test, an FOBT test, and colonoscopy; right?

22 A I do, yes.

23 Q And so if you look under Study Design, for the
24 DNA test, which is described in the second

1 sentence, "The subjects were instructed to
2 collect a single whole stool using a plastic
3 bucket-type container that could be mounted on a
4 toilet seat and sealed with an airtight lid.
5 Samples are shipped directly from home using a
6 courier service within 24 hours of collection."

7 Do you see that?

8 A Yes.

9 Q So would you agree with me for the DNA test of
10 this, it involved direct defecation into a
11 bucket, sealing the bucket, and shipping it back
12 to the lab?

13 A Yes.

14 Q So there was very little, if any, fecal
15 manipulation involved in that process?

16 A It appears to be so, yes.

17 Q And then it says for the FOBT, this is the
18 immediately following sentence, "For FOBT,
19 subjects were instructed to implement dietary
20 restrictions specified by the manufacturer and
21 discontinue use of aspirin and other
22 nonsteroidal anti-inflammatory agents for
23 greater than 72 hours before collecting two
24 smears from each stool on three consecutive

1 days. Once completed, the hemoccult II were
2 returned to the participating cite for
3 processing in a prepaid, pre-addressed
4 envelope."

5 Do you see that?

6 A Right.

7 Q You'll agree with me that what's being looked at
8 here is a gFOBT test; right?

9 A I think so.

10 Q And this gFOBT test requires pairing,
11 smearing -- scratch that.

12 This gFOBT test involves preparing --
13 collecting two smears on -- from each stool on
14 to a hemoccult II card on three consecutive
15 days; right?

16 A Right.

17 Q So would you agree with me that -- with me
18 there's a relatively high amount of fecal
19 manipulation involved in this gFOBT test?

20 MS. FERNANDS: Objection. Form.

21 THE DEPONENT: I would say so.

22 BY MR. JONES:

23 Q Then the third test would be -- the third thing
24 that was evaluated were colonoscopies; right?

1 A Correct.

2 Q And for the colonoscopies, the subjects
3 underwent bowel preparation, as recommended by
4 their endoscopist, and then went -- underwent
5 colonoscopy; right?

6 A Right.

7 Q You'll agree with me that no FIT test was
8 evaluated in this paper; right?

9 A I don't think so.

10 Q If you look at the Results section of the
11 abstract, it says, "A total of 4,042 subjects
12 completed the survey. 84 percent response
13 rate."

14 Do you see where I am?

15 A Yes.

16 Q The SB DNA testing received the same or higher
17 mean ratings than FOBT for most prep and
18 test-related features.

19 Do you see that?

20 A Right.

21 Q "And when compared to colonoscopy, SB DNA
22 testing receives higher ratings for all prep and
23 test-related features, except perceived
24 accuracy, where colonoscopy was rated higher."

1 Do you see that?

2 A Right.

3 Q Then this last sentence says, "Overall, a higher
4 percentage of patients preferred SB DNA testing;
5 45 percent to both FOBT, 32 percent for
6 colonoscopy; 15 percent for routine screening.
7 8 percent had no preference."

8 Do you see that?

9 A Right.

10 Q So you'll agree with me that despite the high
11 amount of fecal manipulation involved in the
12 gFOBT test, almost a third of these patients
13 still preferred that gFOBT test over the DNA
14 test?

15 A Can you point out where this data is?

16 Q So the last sentence of the abstract results.
17 It says, "Overall, a higher percentage of
18 patients preferred the SB DNA test, testing
19 percentage, parenthesis, 45 percent to both
20 FOBT, parenthesis, 32 percent in colonoscopy --
21 15 percent."

22 So of the 4,000 subjects tested, 45 percent
23 of them said they preferred the DNA test; right?

24 A Right. Yeah. Right. So 45 percent said that

1 they preferred FOBT to -- I'm sorry. 45 percent
2 said they prefer DNA testing to FOBT and
3 colonoscopy. 45 percent of them said so.

4 Q And 32 percent said they preferred FOBT tests to
5 DNA testing and colonoscopy?

6 A Right. Yeah.

7 Q So of the 4,000 subjects who completed the
8 survey, you'll agree with me that over a
9 thousand of them said, "Of these three options,
10 I prefer the FOBT test."

11 Right?

12 A Yes.

13 Q And will you agree with me that the FIT test
14 described in Vilkin involves less fecal
15 manipulation than the gFOBT test described in
16 Schroy?

17 A I agree with that. It requires --
18 quantitatively, it requires less manipulation.

19 How significant this difference in
20 manipulation is I can't comment on it because it
21 was not compared in the studies. I cannot
22 really say how impactful the particular added
23 manipulation. That is in Schroy study versus
24 Vilkin study.

1 But quantitatively, yes, there's more
2 manipulation.

3 MR. JONES: Why don't we take a break.

4 (Break.)

5 MR. JONES: I have no further questions for
6 the witness.

7 MS. FERNANDS: I actually have just a
8 couple very quick questions for the witness.

9 EXAMINATION

10 BY MS. FERNANDS:

11 Q Earlier, there was a question where you were
12 asked -- and I believe the terminology was
13 whether Lehnard included a blood protein test.

14 Do you recall that?

15 A Right.

16 Q And do you have Lehnard in front of you?

17 It's Exhibit 1004.

18 A Yes.

19 Q And the fecal occult blood test in Lehnard on
20 page 4, that's a gFOBT test; correct?

21 A Yes.

22 Q GFOBT tests for heme, H-E-M-E; is that right?

23 A Yes.

24 Q Is heme a blood protein?

1 A No, it's not. GFOBT does not test for blood
2 protein. It's a test for heme, H-E-M-E.

3 MS. FERNANDS: That's all I have for
4 questions.

5 MR. JONES: No questions.

6 (Signature reserved.)

7 (Deposition concluded at 3:30 p.m.)

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CERTIFICATE

I, Richard D. Ehrlich, a Certified Shorthand Reporter of the State of Illinois, do hereby certify that I stenographically reported the proceedings had, and that the foregoing transcript is a true and accurate record of the proceedings had therein.

IN WITNESS WHEREOF, I do set my hand this 20th day of January, 2025.



Richard D. Ehrlich
Certified Shorthand Reporter
License No. 084.2019

1 Anastasia M. Fernands

2 anastasiafernands@quinnemanuel.com

3 January 21, 2025

4 RE: Geneoscopy, Inc. v. Exact Sciences Corporation

5 1/15/2025, Dr. Vadim Backman (#7096020)

6 The above-referenced transcript is available for
7 review.

8 Within the applicable timeframe, the witness should
9 read the testimony to verify its accuracy. If there are
10 any changes, the witness should note those with the
11 reason, on the attached Errata Sheet.

12 The witness should sign the Acknowledgment of
13 Deponent and Errata and return to the deposing attorney.
14 Copies should be sent to all counsel, and to Veritext at
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16 Return completed errata within 30 days from
17 receipt of testimony.

18 If the witness fails to do so within the time
19 allotted, the transcript may be used as if signed.

20
21
22 Yours,

23 Veritext Legal Solutions
24

Geneoscopy, Inc. v. Exact Sciences Corporation

Dr. Vadim Backman (#7096020)

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Dr. Vadim Backman

Date

1 Geneoscopy, Inc. v. Exact Sciences Corporation

2 Dr. Vadim Backman (#7096020)

3 ACKNOWLEDGEMENT OF DEPONENT

4 I, Dr. Vadim Backman, do hereby declare that I
5 have read the foregoing transcript, I have made any
6 corrections, additions, or changes I deemed necessary as
7 noted above to be appended hereto, and that the same is
8 a true, correct and complete transcript of the testimony
9 given by me.

10
11 _____
12 Dr. Vadim Backman

_____ Date

13 *If notary is required

14 SUBSCRIBED AND SWORN TO BEFORE ME THIS

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&	1006 3:17	156:18	2017 21:9,23
& 1:17 2:10 37:16,19	142:20 143:3	20 38:13 77:24	22:5
0	10th 33:19	147:24 167:15	2019 34:6
0.7 81:16 82:19	11 29:13,15,20	2001 6:13 18:4	2021 3:7 6:2
02210-2600 2:5	11,634,781 1:8	18:6 26:16	2022 3:9 5:23
084.2019	7:9	2002 41:2	6:3 27:17 44:9
164:14	11,970,746	2003 41:2	2023 10:19,20
1	31:11	2005 106:3	11:16,17,19
1 67:5,6 86:20	112 144:4	107:5 111:14	12:7 14:5 22:7
92:5,22 93:16	154:1,4,9	111:18	22:11
101:20 102:14	116 146:9	2006 37:4	2024 10:11
126:24 127:4	119 3:14	40:12 41:3	11:23 13:3,22
1/15/2025	11th 33:14	42:9	13:23 16:3,6
165:5	12 44:6	2007 43:14	17:13 22:8,12
10 33:1 66:8	12:21 90:21	2008 3:10	22:15,18,22
67:17,19 70:15	13 44:12 149:8	69:14,18,20	23:2 24:13,14
70:17 81:16	130 29:11	70:17	24:20 33:1,14
82:24 95:3,9	142 3:17	2009 18:6	2025 1:18
97:1	143 94:20	19:14 20:7,17	164:9 165:3
10,000 86:18,19	145 95:21	21:11,13 46:14	2048 3:19
87:15 89:2	147 94:5	46:21,22 47:7	155:20,22
100 28:15,16,18	148 97:17	57:13,14,16	156:4
28:24 29:1,7	15 38:13 160:6	58:24 59:9	20th 50:17
29:10 117:19	160:21	64:14,24 67:23	164:9
139:21	155 2:5 3:19	80:8	21 165:3
10010 2:11	15th 1:18	2012 36:9	212.849.7000
1004 3:12 91:3	162 3:4	2014 21:22	2:12
91:6 162:17	17 46:14	53:2,5 54:12	2171 164:12
1005 3:14	18 51:9	54:18,22 55:14	22nd 2:11
119:16,19	18,919,170 31:1	57:13 58:22	23 91:14
120:5	2	59:14,21 60:2	23.8 72:1
	2 83:5 90:2	63:16 69:15	24 157:6
	101:20 108:7	79:21,22 80:8	2524 132:2
		81:1	

28 10:22	5	72 157:23	89 118:5,18
3	5 32:23 57:1	72.5 146:21	119:7
3 76:10,24 79:2	66:8 78:9	147:9 148:12	89.3 147:17
80:9 90:6	148:2	148:22	89.8 118:17,18
101:20	50 27:16	73.8 71:7,11	119:8
30 44:11,19	51 2:10	77:24	9
165:16	52 146:15,20	74 143:1,10	9,989 86:24
32 160:5,20	147:2,9	746 31:11,14,17	90s 37:21
161:4	55 91:13,15,20	32:2,7	90th 139:24
35 142:24	57 87:3	76 140:1	91 3:12
3:30 163:7	5:00 25:23	153:11	92 56:2
4	6	781 7:12,15	92.3 55:15 71:7
4 3:3 129:4,16	6 3:7,9 30:21	13:7 14:15	71:10 78:1
162:20	156:12	17:6,9,14 21:4	94 146:16
4,000 160:22	60 86:22	21:5,8 30:8	147:3 152:5,7
161:7	617.832.1000	31:17,19 32:2	152:7
4,042 159:11	2:6	32:3 53:14	94.0 72:19
40 46:12 56:19	63 62:23	8	94.4 147:17
57:22 67:18	64 118:21	8 77:21,21	94.4. 152:8
41 52:20 54:23	65 87:12,13	119:10 160:7	95 102:15
55:3 63:7	102:14 116:9	8,000 15:8	116:10,15
69:21	119:7	80 27:23 57:22	150:2,3
42 26:24 27:1	65.7 86:24	95:4	98 119:3
56:20	69 3:10 120:2,7	80th 56:21	9:00 1:19
42.4 71:24	7	82 149:3,10	9:30 25:22
72:11 78:13,14	7 67:22 77:21	152:10	9th 33:22
44 119:3	81:15,16,17	84 159:12	a
45 17:2 25:11	86:16 87:2,3	86 56:3	a.m. 1:19
25:12 160:5,19	156:12,18	86.6 55:16,22	ability 69:9
160:22,24	7.6 87:3	72:19	73:16 80:17
161:1,3	7096020 165:5	86.9 148:22	81:2
	166:2 167:2	87.5 149:3	able 20:8 46:17
			46:24 70:8

85:16 96:24 100:24 147:23 150:4 above 53:4 83:15 94:7 102:15 116:10 126:12 165:6 167:7 absolutely 64:15 89:17 130:23 abstract 56:18 57:6 64:8 86:23 99:6 120:12 122:1 148:5 159:11 160:16 acceptability 154:8,17 acceptable 79:16 acceptance 154:11,21 account 102:6 accounts 28:16 accuracy 90:19 159:24 165:9 accurate 164:7 accurately 76:4 82:6 achieve 50:5 88:10 103:13 achieved 55:15 147:15	acid 17:19,23 19:11 21:19 54:21 106:15 112:22 113:11 113:12 145:20 acids 18:23 113:19 acknowledge... 167:3 acknowledg... 165:12 acquire 42:12 acquired 21:3 acquisition 21:24 22:3 acronyms 121:21 actionable 67:2 active 18:2,10 130:13 activity 130:16 actual 40:11 41:2 50:9 66:1 67:9 actually 15:24 19:7,19 24:12 38:19 44:11 49:22 51:13 69:6 75:7 92:22 100:13 102:10 111:2,7 114:19 116:15 116:23 119:9 130:10 133:24	136:2 138:21 146:22 151:24 156:18 162:7 add 74:23 104:16,20 109:17 114:2 154:22 added 140:5 161:22 adding 107:8 108:18 109:8 111:20 140:3 addition 103:14 additional 29:21 98:5,24 104:17 106:20 140:3 additions 167:6 additive 132:11 address 49:2 65:18 126:17 126:18 133:18 133:24 addressed 158:3 addresses 126:2,9,12 adenocarcino... 80:18 adenoma 61:2 86:11 108:8 111:21 153:4,8 153:9	adenomas 48:5 50:11 55:9 56:9,14,19,23 57:10,21 58:5 58:7,13,17 59:7 60:14,15 60:21 61:1 62:3,9,20 63:3 64:5,15 65:3 65:14 66:14 67:4,12 68:2,7 72:6 73:16,19 73:21 78:4,21 79:17 80:3 81:15,16 82:23 83:3 85:2,10 85:11,20 86:7 87:4 89:16,22 89:23 90:3,8 90:14,19 98:8 103:2,2,11 107:22,24 108:10 122:6 140:1 adequate 116:5 administer 137:5 administered 51:24 advance 29:16 advanced 50:10 55:9 56:9,14,19,23 57:9,21 58:5,6
---	---	---	--

58:13,17 59:7 60:14,15,21 61:1,2 62:3,9 62:19 63:3 65:2 67:10,11 68:2,7 71:23 72:4,5,9 73:16 73:19,20 75:10 75:20 77:1 78:4,21 79:17 80:3 81:15 82:23 83:3 84:7 85:2,9,11 85:20 86:6 87:3 89:16,23 90:3,14,19 103:2,2,11 107:22,24 108:8,10 111:21 122:6 140:1 153:4,8 153:9 advantage 71:20 77:13 114:19 125:5 125:10 152:18 152:19 advantageous 124:14 advantages 75:11,21,23 79:10 106:24 121:10 123:16 123:24 152:12	adviser 68:1 advisors 39:14 affect 130:17 affiliated 143:22 affiliation 34:11 143:20 agents 157:22 aggressive 60:22 78:18 ago 9:8,9 24:9 24:11 37:20 38:3,4,8,13 agree 45:4,10 46:1 62:7 68:9 69:1 70:23 71:4,12,18 72:4,23 73:22 88:4 92:14 93:10 95:7 96:1,4,5 107:5 107:8,11,18 115:2,7,8,15 120:23 121:15 121:20 122:22 123:1,2,5 124:4,13 125:4 125:14 126:5 127:3,9 128:19 129:18 133:5 134:14 135:9 135:18,23 136:10,19 137:1,9 138:22	144:7 145:14 146:2 156:19 157:9 158:7,17 159:7 160:10 161:8,13,17 agreement 22:24 ahead 23:3 140:11 aim 83:24 84:5 84:9,16 87:16 87:17,21,24 88:1,9,9,11,19 88:22 89:3,4,8 89:9,12,18 90:11 aims 84:5 88:4 90:13,13 airtight 157:4 ajcc 80:20 al 55:13 91:9 119:21 143:5 alerted 15:22 algorithm 49:16 aliquoted 95:4 95:15 96:19 97:9,11 aliquots 97:12 allotted 165:19 allow 98:7 99:1 allowed 59:24 94:1	allows 121:6 123:11 130:11 alterations 41:19,20,20 alternative 51:6 56:5 alternatives 46:17,24 47:6 51:9,17 52:7 american 36:21 36:24 37:12 80:20 amount 67:8 128:20 145:23 158:18 160:11 amounts 67:17 analogous 84:14 analysis 3:12 28:10 35:10 41:14,15 43:17 52:2,3,10 54:24 55:5 76:12,13 90:2 91:9 94:1 97:9 104:13 131:7 136:23 137:2 137:21 141:18 142:10 analyze 42:17 43:1,16 analyzed 35:8 35:16 97:10,13 100:4 105:16
--	---	---	---

analyzing 41:16 42:3,9 42:13,20,22 43:6,12 anastasia 2:9 3:4 25:1,2,17 25:18 26:1 165:1 anastasiafern... 2:12 165:2 anesthesia 49:21 animal 42:14 122:13,16 animals 42:15 announced 53:9 annual 132:10 132:22 135:2,5 135:18,21 136:2,4 140:8 140:24 141:10 anolytes 43:20 answer 4:22 5:15 14:22 15:3 16:2 23:22 32:21 33:20 74:19 89:17 134:4 139:6 144:15 answered 29:4 answering 4:15 answers 5:18	anti 157:22 anybody 16:22 59:12 81:22 142:6 anyplace 104:24 apologize 22:13 appeal 1:2 appeared 15:11 appears 22:1 96:23 157:16 appended 167:7 apples 112:18 applicable 165:8 application 20:6 30:24 31:1,4 applications 31:18 32:1 appointment 18:4 approach 48:13,14 51:15 100:6 103:24 approaches 47:16 48:21 49:3 51:18 52:19 60:6 63:15 appropriate 45:14 47:13 85:5 113:22	appropriately 89:10 approval 85:8 112:5 114:9,10 approved 114:15 approximate 16:24 17:3 43:11 approximately 28:8 87:14 area 15:17 57:3 60:10 77:7 103:5 areas 101:16 argue 133:11 arguing 13:8 argument 104:1 arithmetic 110:13 arrive 142:11 arrived 152:9 art 30:1,14 article 14:10 55:13 aside 39:24 75:9,19 asked 11:24 12:6,9,11 14:12,12,20 15:3 17:10 20:13 46:5 75:14 162:12	asking 12:11,13 15:23 68:13 124:18 138:8 asp 34:2,3,6,11 34:15,18,21,23 34:24 35:13,20 35:24 aspect 17:14,17 152:14 aspects 13:14 14:15 15:10 141:23 aspiration 35:5 aspirin 157:21 assay 46:3 54:17 92:9 96:16 103:18 103:19 106:21 106:22 107:9 107:12,13,23 126:9 127:6 138:16 144:8 145:22 147:23 148:11,16,17 149:6,12 150:9 150:20 152:5,9 152:11 assays 51:6 94:10 107:6 122:13 123:17 124:2,3,7,16 145:10,15 149:20 153:4
---	---	--	---

asserted 7:16	australia 135:5	31:6,9 34:2,5	54:2 68:21
assessed 76:5	135:11	35:22 36:21	72:11 74:15
assessment	author 21:21	37:7,12 75:11	84:16,17 87:7
101:10 142:5	143:20	75:21 79:24	87:8 88:23
assistance 27:6	authored	131:15	98:2,8 99:12
28:2	143:13	b	101:18 104:12
associated	authors 70:6,9	b 3:6 77:1	104:13 119:1,9
122:23	91:22 93:18	100:10 105:22	127:13 130:7
assume 59:13	94:9,14 100:19	110:2 113:1,8	135:15 136:22
86:1 88:9	132:16,24	113:13	139:10,11
144:24	135:1 143:18	back 10:19	140:9 150:22
assumption	143:21,22	19:13 20:1,1	basement 66:4
145:5	automated	22:6 27:14	basic 19:17
assure 64:14	3:15 119:22	34:23 35:12	began 52:15
asterisks	121:3 123:7	37:3,5,21 55:2	beginning 18:7
143:21	124:1 126:8	65:5 66:9 71:3	91:19
asymptomatic	automatically	79:11 106:2	begins 97:19
73:8 133:14	81:10 82:22	120:9 124:5	behalf 2:3,8
134:11 146:17	available 43:8	144:1 157:11	21:13 34:15
attached	43:16,23 48:19	backman 1:14	36:19
165:11	48:19,20,22	3:8,9 4:1,4	belief 59:3
attempts 51:20	63:17,23 107:6	91:2 165:5	believe 10:17
52:1	111:22 113:6	166:2,24 167:2	21:22 22:21
attended 16:9	113:22 165:6	167:4,12	25:5,22 36:8
attention 27:17	avenue 2:10	bad 103:10	40:11 43:18
120:9	average 67:18	bags 129:1,13	51:8 52:7
attorney	73:9 110:13	balance 76:16	56:11 62:11,23
165:13	135:3 136:15	101:13	64:9 69:15
attorneys 16:17	141:19,24	ballgame 66:11	70:3,5 71:2
attributes	142:7,14	barium 48:13	73:18 74:10,11
67:14 69:7	146:17 152:5	barnes 1:16	75:2,7 76:7
auc 15:17 57:3	aware 9:20	based 47:18	77:20 78:14
77:8 82:2	16:22 20:23	48:16 52:5	92:6,24 95:10
101:24 110:5	21:12,24 30:23		107:7 108:8

127:20 128:9 132:22 135:21 141:9 143:15 162:12 believed 105:17 belong 32:19 beneficial 19:23 benefit 48:9 136:16,23 137:2,21 138:2 138:4 141:17 142:1,10 benefiting 109:8 benefits 46:18 47:2 106:20 best 5:10 30:12 35:20 36:10 78:24 103:9 113:5 140:4 better 35:2 40:15 50:9 68:10,15 77:2 77:3,8,16 79:5 80:5 100:6 101:11 102:12 103:9 107:9,12 108:3,5,23 109:1,2,4,5,7 109:21 110:2,2 110:19,20,21 110:22 111:10 111:11 112:13	113:20 114:4 114:11 116:24 124:19 130:11 147:7,22 beyond 150:17 150:18 bi 135:5,18,21 136:2,4 big 79:18 biology 106:16 biomarker 43:8 76:2 77:11 110:23 111:13 111:16 113:12 113:13 114:2 150:10 151:3 biomarkers 18:16,23 19:12 22:4 39:8,22 41:9,16,21 52:3 54:21 87:10 113:11 150:14,21,23 151:2,20 152:15 biooptics 36:22 37:1,13 biostatistics 76:2 109:22 bit 129:9 bjones 2:6 blood 3:15 18:22 19:11 48:18,20 51:7	52:3,3 55:1,6 56:24 91:24 92:8,14 95:23 96:1,3,6,12 119:23 120:17 122:3 132:12 153:17 155:7 155:16 162:13 162:19,24 163:1 board 1:2 34:10,13 board's 32:23 bodies 68:1 85:15 body 18:15 97:17 121:23 borrowed 28:11 boston 2:5 bottom 46:14 93:16 boulevard 2:5 bowel 49:20 159:3 break 5:9,10,12 5:12,15 44:2,4 90:23 119:14 119:15 162:3,4 breaks 25:23 breast 35:6 brendan 2:4 3:3	brief 38:2 bring 35:12 broader 134:15 brought 5:21 97:8 bucket 157:3 157:11,11 buffer 43:24 128:8 144:19 154:23 buffers 43:19 43:22,23 build 146:13 c c 2:1 95:4 113:14 cahn 10:17 11:3 12:4,10 22:10 calculated 102:1 calculations 87:8 call 7:12 16:12 16:13 48:23 76:6 94:14 109:15 112:24 119:10 121:16 127:5 called 20:20 21:13 34:2,20 35:3 36:2,21 40:17 70:3
--	---	--	---

86:12 95:22 110:9 126:22 calls 13:23 24:23 121:13 cancer 3:13,17 11:10 18:2,15 18:20 19:1,2 35:6 39:7,8,21 39:21 45:4,7 45:16 46:2 50:21 55:20,23 58:4,20 61:1,9 62:18 63:18 66:1,2,10 67:10 68:10,11 68:14,19,20 69:2,6,10 71:6 71:16,20 72:24 73:9 75:10,20 80:18,20 81:2 81:14,16,19 84:2,12 85:1 86:11 87:3,16 91:11 92:15,23 93:2,6 94:17 98:2 106:7,8 115:4 117:18 118:9 120:14 120:18 122:5,6 133:6 134:17 143:6 146:17 152:22 cancers 50:10 50:22 65:19	67:11 73:11,20 76:24 77:23 78:20 82:18,21 83:2 85:10,12 85:13,17,18,21 86:6,15,21 87:14,19 89:16 90:7,14 93:21 94:3,11 101:4 103:10 115:18 117:10 119:3,6 139:24 candidates 151:3 capsule 50:20 captured 77:4 110:8 captures 76:21 carcinogenesis 40:16,17,19,23 41:10 card 158:14 care 47:22,23 career 18:8 careful 90:2 carefully 27:9 28:5 62:12 case 1:6 12:2,8 13:1,5 14:17 52:10 82:18 86:13 87:23 110:20 111:12 112:18 117:23 118:4 127:20	130:4 134:15 135:24 137:3 cases 66:7 82:7 82:10 86:15 87:12 88:23 102:5 108:13 110:7,8 111:1 111:7 categories 113:17 cathartic 94:22 caution 13:17 26:6 caveat 5:13 caveats 115:21 celcius 129:16 cell 41:13 cells 35:14 41:15 66:2,3 center 96:23 153:15 155:6 centimeter 78:8 central 81:20 certain 52:15 82:6,7 130:9 130:12,14 151:16 certainly 45:19 46:7 58:6 88:12 certainty 16:7 certificate 164:1	certified 1:16 164:3,14 certify 164:4 chance 4:19 59:3 66:1,24 67:18 68:22 78:12 151:12 change 60:7 166:4,7,10,13 166:16,19 changed 63:17 102:10 changes 165:10 167:6 characteristic 102:2 characteristics 3:14 67:15 84:1,10 100:5 101:24 102:9 119:21 151:8 151:18 check 16:15 118:6,11 chemical 130:10 chemo 65:23 66:8 chemotherapy 65:22 chicago 1:17 choose 58:2 86:12 126:14
---	---	--	---

chosen 136:14 141:22 chromatin 41:20 circulate 67:10 cite 30:24 69:21 158:2 cited 3:19 26:12 30:9,11 30:17 156:5 cites 153:20 claim 85:17 claimed 53:13 claims 19:17,18 clarify 5:5 7:23 31:22 42:10 43:3 68:5 124:23 134:3 clean 6:5,6,8,9 23:22 clear 29:5 33:8 35:17 45:19 58:11 90:12 105:11 106:23 116:22 clearly 15:8 56:4 68:19 69:3 77:2 89:20 133:21 clients 39:3,17 clinic 48:22 82:8 clinical 15:13 19:4 41:12	46:18 47:1 66:23 69:8,24 80:1,24 81:6,7 82:8 83:1 84:15,22 85:4 85:6,6 88:11 88:16 89:9 97:7 112:9 114:5,8,8,10 132:11 138:16 clinically 66:6 66:22 67:7,21 78:24 79:16 114:13,21 close 17:2 25:23 87:1,5 closed 129:1,13 closer 48:1 coin 78:11 coincided 101:2 coined 102:3 110:10 colleagues 54:3 collect 41:7 137:10,24 138:14 157:2 collected 43:9 94:22 97:4,8 128:14 129:20 144:9 collecting 74:12 131:1,5 132:10 139:13	139:16,18 140:8 157:23 158:13 collection 74:7 74:9 130:13 135:3 144:5,10 144:18 146:3 157:6 collections 127:21 141:8 colloquial 88:13 89:12,18 90:13 98:22 colloquially 88:8 cologuard 51:10 52:22 53:2,8,10 54:12 55:3,15 55:19 56:8,13 57:9 59:15,22 59:24 60:4,5,9 61:4,15,19,23 62:8,17,19,24 63:2,17,23 64:2,4,6,13 65:2 70:1 71:1 71:7,13,15,19 71:20 72:8 73:1,22 74:8 74:13,16 75:5 75:11,22,24 77:3,9,13 78:13 80:24	84:11 112:9,14 118:9,12 119:8 146:5 cologuard's 55:22 58:18 62:2 73:16 118:16 colon 11:10 18:2,20 48:1,2 48:4,7 49:10 49:14,19 61:1 61:8 66:10 69:1 82:18 83:2 85:17,18 92:15,23 93:2 93:6 colonocytes 41:8 colonoscopies 45:1 134:21 158:24 159:2 colonoscopy 11:9 45:13,15 46:14,22 47:7 47:8,13,15,19 48:6,8,10,11,16 49:23 50:15 51:24 60:24 65:1,9,11,13,15 65:18 66:13,18 67:10,20 68:3 81:21,22 86:9 94:23 97:5 118:16 121:7
--	---	---	---

123:13 134:24 153:17 155:8 155:17 156:21 159:5,21,24 160:6,20 161:3 161:5 colorectal 3:13 3:17 40:16 45:4,7,16 46:2 50:9 55:19,23 58:3,19 62:17 63:18 65:19,19 68:10,11,14 71:6,16,19 72:24 73:9 75:9,20 76:24 80:18 81:2,13 81:19 82:21 84:2,12 87:2 87:13,14,15 91:11 93:21 94:2,11,17 98:2 115:4,18 117:10 118:9 120:14,18 122:5,6 133:5 143:6 146:17 152:21 column 93:17 95:22 123:7,24 124:5 132:5 146:12 combination 17:18,22 21:18	43:23 45:8,12 51:22 54:24 55:5 56:1 60:11 65:22 76:1 93:24 94:9 98:5,11 98:19,23 99:5 99:20 100:3 102:11 105:1 107:2 108:3,20 108:24 109:3,3 109:13,16,21 111:1 112:22 114:18 115:7 115:10,16 116:1,13,14,18 116:23 117:7 118:20 119:4,7 149:1 150:10 150:13 combine 19:10 99:14 100:7 104:8 105:24 106:17,19 110:15 112:20 151:3 combined 15:19 19:22 28:13 99:7 100:24 107:11 107:23 110:12 112:10 113:2 113:19 118:4 144:18	combines 110:4 151:10 combining 14:9 18:21 22:4 54:20 103:17 103:23 110:20 111:1,6 come 58:17 66:9 80:5 86:9 97:3,7 133:13 134:6 coming 32:15 commencing 1:18 comment 161:20 commercial 36:14 51:5 commercialize 112:5 commercially 43:22 107:6 111:13,17,18 111:22 113:6 113:21 committee 18:10,14 80:20 communicate 12:21 communicati... 11:21 12:5,14 companies 80:4 company 10:18 20:20 21:13	34:2,7,7,14,18 34:20,22 36:1 36:4,12,13,16 36:21 37:2,4 comparable 118:14 comparator 82:5 113:5,9 compare 60:3 61:4 63:11 100:18 109:20 111:10 118:13 118:18 compared 56:4 56:23 57:24 77:21 99:4 102:19 112:10 114:20 152:1 159:21 161:21 comparing 74:11 112:17 131:7 150:16 150:18 comparison 60:5 63:12 108:4,5,19,23 113:4,21 138:20,22 150:20 151:2 151:18 comparisons 152:2 competitively 151:24
---	---	--	--

complete 4:15 5:17 16:7 167:8 completed 158:1 159:12 161:7 165:16 completely 65:23 66:11 complex 130:12 131:12 complexity 74:24 103:19 109:11 125:20 140:6 compliance 74:18 comprehensive 41:18 concern 7:9 concerned 19:14 23:9 concerning 22:16 32:7 concerns 15:16 concluded 163:7 conclusion 73:3 73:6,15 99:5 99:18 100:5,9 100:12,14 103:22 104:2 104:13,14,16 105:1,9,12,22 107:3 139:12	140:19 142:14 149:19 150:5 conclusions 100:16,18,18 100:19 105:7 condition 82:15 85:1 87:19 conditions 131:22 conducted 81:18,20 confidence 102:15,16 116:11,12,15 149:24 150:3 confirmed 132:11 151:9 confirms 154:23 confused 49:15 65:8 74:2 confusing 136:3 consecutive 137:11 138:15 138:18,19 139:7 141:4,8 157:24 158:14 consequence 77:15 consider 17:22 32:6 55:22 56:1	considerably 152:13 consideration 76:16 90:4 102:23 106:13 137:3,6 considerations 61:17 62:22 63:24 64:21 103:21 137:7 138:2,3 considered 29:21 32:13 60:21 67:7 156:8 considering 19:5 74:20 115:20 consistent 136:7 constituted 56:22 constructed 15:9 consult 39:1,16 consultant 37:15,18,22 38:1,9,20,23 39:5,10,13 consultants 38:16,22 consultation 38:19	consultations 12:17 consulting 37:23 38:10,15 39:19,23 40:1 40:3 contact 11:2 contacted 10:14 22:10 38:18 container 127:11,17,19 127:24 128:3,7 128:10,15 145:1,9 157:3 contains 128:7 contamination 128:1 context 79:12 79:13 88:19 99:12 135:23 136:9 138:3 151:14 continuation 30:24 continue 132:9 133:1 140:8,20 141:1 continuing 132:16 contract 10:12 contradict 112:2
---	--	---	--

contrast 135:2 control 86:13 controls 102:5 110:8 convenient 73:23 74:8 conventional 88:13 conversation 13:18 conversations 12:9 23:5 54:2 conveyed 4:11 copies 155:23 165:14 copy 6:5 17:8 156:1,2 corporation 1:8 165:4 166:1 167:1 correct 4:9 6:1 6:18 7:10,11 8:8,19 9:3,4 11:16,17 25:7 26:3 27:2,8 28:1,4 29:9 30:15 31:13 39:15 40:22 53:1,3 55:11 57:4 61:18 69:23 70:2 71:10,17 84:4 84:13 91:21 92:4 95:13	108:2,4,5,13 111:19 121:12 121:17 122:15 124:12 130:22 133:3 134:19 139:4 141:20 143:11 147:11 148:4,24 149:5 152:11,24 153:10 159:1 162:20 167:8 corrections 167:6 correctly 20:9 53:22 113:4 137:15 correlate 41:11 correlation 45:19 cost 50:4 51:21 136:16,23 137:2,21 138:2 141:17 142:1 142:10 148:1 149:8,13 costs 140:5 could've 47:20 counsel 4:11,19 12:23 16:4,6 22:7,11,14 23:5,8,14 24:3 24:4,24 27:4,7 28:3 165:14	count 22:23 28:13 countries 135:10 140:13 140:15 country 117:17 couple 9:8 12:15,23 24:5 24:9,10,12 25:23 76:11 147:12 162:8 courier 157:6 course 18:11 21:20 41:1 48:19 60:10 66:19 117:23 132:17,20 134:21 141:5 court 4:17 5:1 7:17,22 8:3,21 9:21 33:15,23 crc 46:15,23 47:9 55:16 98:8 115:24 117:16 crcs 55:8 59:14 63:1,3,8,20,21 64:4,15 89:22 101:1 102:14 117:15 139:21 create 106:8 147:23 created 97:12	criteria 61:5 103:15 critical 17:17 46:7 69:13 77:5 103:12 115:20 crucial 69:7 cs 165:15 ct 48:15 ctc 48:15 49:11 cumulative 110:4 cumulatively 28:17,23 29:7 curative 65:16 current 36:11 currently 36:18 37:15,22 39:13 51:12 56:6 79:23 140:12 curve 15:18 57:3 60:11 76:6,7,19,21 77:7,16 79:2 101:16,17 103:5 curves 77:2,2 90:7 cut 101:9 cutoff 76:19 77:16,19 cytologist 35:8
--	--	--	--

d	167:15	58:15 59:1,6	dependent
d 3:1 40:21	days 35:11	59:11 61:21	110:6
164:3,13	130:3 132:21	62:1,2,10	depending
dangerous	137:11 138:15	64:18,19 69:22	67:13 118:13
60:22	138:18,19	91:14 118:22	135:23
data 15:16 16:1	139:7 141:4	120:3 142:24	depends 74:19
28:10 42:22	158:1,15	143:9 153:12	76:18
43:1,6,8,9,12	165:16	154:2 156:9	depiction 127:4
43:16 52:5	deal 14:23	declarations	deponent 4:1
74:11 75:7	67:11 79:18	7:8 8:1,4,11,23	26:8 44:3 46:5
76:8 85:7 90:1	dealing 81:23	9:18,24 26:12	53:17 58:22
100:17 101:7	deals 133:16	28:17,23 29:7	68:13 74:1
101:17,18,23	death 45:18	declare 167:4	88:7 92:18
103:23 104:13	decade 38:5,7,9	decrease	105:5 112:1,17
105:1,16,16,17	december 12:7	147:16 148:2	115:15 123:20
105:21 114:10	24:14,20,21	decreasing	124:18 125:9
114:16,17	decided 136:22	149:9	127:13 128:13
115:16 116:4,8	decision 19:10	deemed 167:6	129:23 133:10
117:10 119:1	32:24 136:12	deep 70:3	135:15 137:1
129:24 133:10	140:9 141:15	default 85:1	137:14 139:10
139:11 140:10	142:18	defecate 97:8	146:7 152:24
140:17 151:5,7	declaration 3:8	defecation 95:3	158:21 165:13
160:15	3:9 5:23 6:5,14	95:9 127:15	167:3
date 21:23 22:2	8:7,17,18,20	144:10,17	deposed 4:6
22:3,23 36:8	22:17 26:15,16	157:10	deposing
60:7 61:8	26:21,21,24	define 82:5	165:13
63:22 130:7	27:3,9,13,18,20	107:15	deposit 35:14
166:24 167:12	27:24 28:2,5,9	definition	deposition 1:14
day 1:18 19:13	28:11,14,20	66:23	9:3,8,11 10:6
20:1 22:24	29:12,13,17,22	degradation	23:4,7,16 24:1
54:14 90:16	30:2,8 31:5,15	107:21 130:14	24:2 26:5
135:3,5,18	31:21,24 44:6	degree 154:24	32:15 33:1,5,9
138:19 164:9	44:9,20 46:12	degrees 129:4	33:13,15,17,22
	56:11,12 57:15	129:16	33:23 163:7

depositions 9:6 33:10	85:17,18,19,21 85:24 87:18	developed 3:15 48:17 50:20	125:15 157:19
depressed 66:15	101:1 107:23 108:2 122:13	114:13 119:22 121:4 123:8	difference 51:13,14 116:2 161:19
derrick 1:15	detected 44:22	124:1	differences 102:6
descending 48:2	45:5,7 50:13 68:11,15,15	developing 35:1,13 43:19	different 28:21
described 81:1 124:2 144:8 156:24 161:14 161:15	73:10 92:15,18 93:2,6,19 108:13,15,16 115:4,5,24	43:21 51:6,20 128:11 129:14 129:19	41:11 52:8,10 52:11 65:23 66:10,11 89:4 89:5 103:19
describes 138:10	detecting 69:1 69:2 71:6,23 115:18	development 48:15 50:20 54:17,17 124:8 125:1,6 129:4 129:16 151:6	111:6 112:21 113:23 114:22 114:23 126:14 131:11 135:10 135:11 140:12 142:13 145:10 150:9,10 152:2
describing 59:21 85:4 114:1	detection 3:13 18:13 35:6 46:2 50:21 52:12 84:2,7 84:11 91:10 94:2,10,17 98:8 108:9 111:21 130:11	device 35:1 127:6,9	difficult 50:23
design 82:13 84:16 89:9 156:18,23	detects 69:6 72:8	dia 148:13 149:2 150:11 150:23	diminishes 111:8
desirable 46:2 46:6,7 125:20	determine 84:1 84:6,9 138:24	diagnosed 45:23 47:10	direct 144:10 144:17 157:10
despite 49:11 80:3 160:10	determines 82:16 84:18	diagnosis 45:20	directions 52:1
detail 59:2 60:10	determined 80:19 137:21 145:20	diagnostic 46:3 46:8 50:8 52:14 65:12,16 68:4 77:6 101:9 112:23 117:8 144:21 145:2,6,11	directly 58:23 157:5
details 11:12 12:2,24 14:14 14:17,17 15:12 41:5 54:8,9 60:8	develop 43:22 45:9 66:1	diet 121:5 123:10	directors 34:13
detect 68:21 69:9 73:16 78:17 80:17 81:2 85:9,11		dietary 122:19 122:22 123:2	disadvantage 114:20 122:24
			disadvantages 109:10 120:24 125:14
			disagree 107:14

disclosed 123:17 disclosures 11:13 discontinue 157:21 discuss 12:8 14:14 17:6,14 53:4 56:11 59:4 60:9 64:13,19 74:10 120:6 125:22 discussed 12:13 15:12 59:1 60:8 62:24 64:17 91:19 discusses 126:8 discussing 120:24 discussion 14:18 57:14 94:8 discussions 22:16 disease 44:22 68:24 69:9 80:19 87:7 dispute 7:2,3 distal 48:3 distribution 110:7 distributions 102:7	district 7:16,22 8:2,21 9:21 33:15,23 divided 95:17 dna 3:17 54:24 55:5 70:24 71:11,12,24 72:16,18 73:10 80:17 83:12,23 84:2,6,10 91:23 92:2,8 92:16 93:1,5 94:15 96:16,21 97:14 112:14 143:5 144:19 145:6,10,15,18 145:21,23,24 146:15 147:6,7 147:22,22 148:9 153:16 154:22 155:7 155:16 156:21 156:24 157:9 159:16,21 160:4,13,18,23 161:2,5 doctors 134:23 document 5:21 5:22 6:12 26:20 27:19 91:4 92:6 119:18 156:13 156:17	documents 5:20 7:21,23 23:19 26:4,11 29:21 doing 36:15 49:21 96:18 106:20,24 109:10 131:6 138:7 140:20 double 60:18 74:3 88:11 129:1,13 143:21 doubling 56:22 78:3 dr 4:4 8:4,6,11 8:14,15,15,17 8:18,24 9:2,5 9:12,15,17,20 10:1,3,7 20:16 20:16 33:2,10 91:2 165:5 166:2,24 167:2 167:4,12 drafted 27:6 drafting 156:9 drive 1:17 109:18 drop 57:1 77:20,21 78:4 78:23 101:2,3 103:7 117:11 149:22 150:14 151:17	drugs 39:8,21 due 67:20 122:7 duncan 30:9 33:2,6 dutch 20:13 54:3 e e 2:1,1 3:1,6 35:3 40:21 162:22,22 163:2,2 166:3 166:3,3 earlier 33:6 41:1 45:24 67:3 106:5 162:11 early 10:11 18:13 22:21 55:8 66:2 69:2 85:24 easier 118:21 easily 67:3 edited 28:12 edits 27:4 effect 102:3,9 102:20,22 110:10,10,12 116:18 131:16 140:4 effective 51:21 efforts 80:4
--	--	--	--

ehrllich 1:15 164:3,13 either 16:13 17:6,13 30:18 49:6 63:1,3 64:4 135:22 eligible 81:22 81:24 133:14 eliminates 121:5 123:10 email 11:4,5,15 11:18 emanuel 2:10 16:17 emphasize 64:16,22 employed 20:16,19 21:1 54:6 143:13 152:1 employees 16:20 70:7,12 70:14 employs 150:21 ended 25:22 28:14,20 endoscopist 65:13 159:4 endpoint 50:12 58:12,16 65:1 68:3 81:6,8,10 81:11,12 84:17 85:2 87:21 103:12	enema 48:14 engaged 13:19 22:20,21 engagement 7:4 12:22 13:22 22:18,23 22:24 england 53:7 55:14 enhanced 148:13 enjoys 49:21 entire 48:7 53:18 entirely 98:12 entitled 119:21 envelope 158:4 enzyme 130:16 enzymes 130:12,13 epigenetic 39:7 39:20 41:19 epigenetics 39:20 106:9 equally 90:14 101:5 errata 165:11 165:13,16 eschoo 9:20 10:1,3,7 esophageal 50:21 especially 18:23 56:3	103:5 127:20 essence 150:16 essential 130:23 essentially 36:13,14,17 48:6,15 57:24 65:15 101:21 102:4,21 estimated 87:7 87:11 et 55:12 91:8 119:21 143:5 evaluate 83:11 83:22 130:5 evaluated 137:20 158:24 159:8 evaluating 76:14 evaluation 3:14 119:22 124:9 125:1,6 136:16 138:23 142:1 evaluations 37:23 38:10 eventful 10:24 eventually 28:14,19 51:11 51:15 59:23 everybody 18:19 19:21 103:12 106:6 106:12 133:23	evidence 107:20,21 exact 1:8 7:6,16 9:20 11:11 16:20,23 19:10 21:1,3,8,16 22:2 27:15 30:23 31:10 32:8 35:21 36:8 37:8,9,10 37:13 40:1 51:10 52:22 53:10,14 54:6 54:7,19 55:4 70:7,10,12,13 70:14,21 71:9 74:18 76:17 118:6,19 143:13,16,22 149:12 153:2,6 156:14 165:4 166:1 167:1 exactly 38:12 104:1 exam 3:3,4 examination 4:2 35:4 162:9 example 35:5,6 47:22 52:9 55:12 59:15,19 61:9 63:9 81:8 85:8 117:23 125:18 130:11 139:1 145:22
---	--	---	--

examples 59:20 76:7,11 131:15 131:18 excellent 55:7,9 55:24 56:4,7 139:20 except 159:23 excess 154:20 exciting 106:10 exclude 98:10 98:13,13,17 99:11 105:7 executives 34:14 exhibit 3:7,9,10 3:12,14,17,19 5:23 6:2,3,13 26:15 27:17 44:9 69:14,18 69:20 70:17 91:3,6 119:16 119:19 120:5 142:20 143:3 155:20,22 156:4 162:17 exhibits 30:7 existed 52:5 56:5 58:1 80:7 existing 36:12 exists 56:6 58:1 expect 74:17 75:3 expense 147:16 151:16	experience 12:16 40:6 42:20,22 43:5 43:19 154:21 experimental 46:16,24 51:9 51:15,17 52:6 52:18 63:14 experiments 43:21 expert 6:19,22 7:1,4 9:21 10:10,15,18 11:8 117:24 expertise 11:11 12:16 13:11 14:6 experts 8:2 19:24 67:24 explain 61:6 explains 95:7 125:13 explicit 33:21 explicitly 62:9 98:17 99:10,11 99:23 104:15 104:16 105:6 105:13,14 exploration 99:14 exploratory 111:15 explore 100:8	explored 105:20 expression 41:24 42:5 extensive 30:19 extensively 59:5,5 extent 32:9 61:23 103:6 extracted 101:17 145:7 145:15,18,23 extraction 147:7,22 extreme 117:22 117:23 extremely 34:24 38:14	fails 165:18 fair 144:24 fairly 15:7 41:18 50:17 57:19 131:8 145:5 false 44:24 73:11 109:17 familiar 9:7 14:8 17:12 32:17 53:19 65:7 142:23 family 21:4,7 30:24 31:19 32:2,9,14,19 far 30:13 48:2 54:4,19 126:19 faster 60:22,23 fault 22:13 faulted 120:19 122:4 124:7 fda 85:15 114:9 feature 46:3,6 featured 57:6 features 46:8 159:18,23 february 10:11 11:23 13:22 21:11,13 22:18 22:21 23:2 fecal 3:15,17 18:22 19:11 40:6,10,14 41:3,17,22
		f	
		f 40:21 121:18 121:19 fact 26:21 58:14 63:22 74:15 79:2 102:20 107:21 109:9 111:3,7 113:7 114:19 122:12 125:17 126:13 151:23 facts 57:18 failed 80:6 151:13	

42:3,5,8,12,15	75:13 88:6	31:6,9	152:18
42:17,20,23,23	92:12,17 105:4	filing 18:7 54:5	fit 15:18,24
43:1,6,12,20	111:24 112:16	final 35:5 97:16	17:18,22 48:19
48:18,20 51:7	115:14 123:19	97:16 152:9	50:3,8,16
52:2,10 54:24	124:17 125:8	find 18:19 48:9	60:19 71:8,11
55:5 56:24	127:12 128:12	56:16 71:9	71:15,19 72:1
95:17,22 96:1	129:6,9,22	77:16 105:23	72:18,23 73:11
96:2,6,9,11,12	133:9 135:14	105:23 132:1	73:23 74:9,13
96:15 119:23	136:24 137:13	139:23 147:7	74:18,20 75:5
120:13,14,17	139:9 146:6	finding 15:21	75:12,22,24
122:3 126:22	152:23 155:10	47:14 146:13	77:3,9,14,22
127:4,5,10	155:23 156:2	findings 41:12	78:8,15 79:5
128:20,21,23	158:20 162:7	99:13 153:14	99:4 112:10,13
131:23 132:10	162:10 163:3	155:5,14	112:21 113:6,7
136:13,14,20	165:1	first 4:8,14	113:13,15,16
137:19 138:15	fetal 40:18	6:14 17:1	113:19,22
140:9 141:15	fewer 151:2	19:17 21:3,8	114:3,4 121:16
141:24 143:5	field 19:1 40:17	22:10 23:1,16	121:20 123:4
144:9,18 145:7	40:20,22,22	24:7,15,22	123:16 126:1,9
145:11,15	57:20 58:11	25:8 26:16,21	131:17,18
146:4 153:16	64:24 67:24	27:13 28:12	132:17,20
153:16 154:22	68:1 76:2	30:5 40:9	135:19 138:10
155:7,7,16,16	79:14 100:1	50:15 52:20	159:7 161:13
157:14 158:18	106:11 109:22	59:21 71:3	fitting 151:12
160:11 161:14	110:23 118:1	80:16 82:9	five 45:20,23
162:19	131:8 133:12	98:20 100:3,17	flat 66:15
felt 20:2 74:12	151:1,15	102:23 112:6	flexible 47:17
100:20	fields 134:5	112:20 116:16	47:24 49:5
fernands 2:9	figure 76:10,24	122:2 124:6	floor 2:11
3:4 13:17	79:2 82:9 90:2	125:13 126:2	fobt 21:18 50:3
23:11 26:6	90:6 126:24	126:10 134:3	50:8,17 54:20
44:14 46:4	127:4	141:13 146:11	92:18,18 93:2
53:16 58:21	filed 7:21 20:6	148:6,6 149:19	93:7,8,9,14
68:12 73:24	21:10,12 30:23	150:6 152:18	94:1,16 96:19

97:10 98:10,14 98:15 99:11,15 100:4,24 101:2 103:17,23 104:21,23 105:2,7,10,15 105:18 107:6,9 107:12,13,23 108:1,3,11,15 108:18 111:20 111:22 112:4 114:11,11,18 115:6,17,19 120:18 121:4 121:11 124:15 124:19 125:7 125:14 140:14 156:21 157:17 157:18 159:17 160:5,20 161:1 161:2,4,10 fobts 63:13 111:18 133:19 focus 19:3 59:10 64:20 79:7,9 focused 58:18 focuses 57:15 folds 49:15,15 foley 2:4 foleyhoag.com 2:6 follow 4:12 123:12	followed 65:21 following 126:5 126:7,7,21 157:18 food 122:17 foregoing 164:6 167:5 form 46:4 53:16 58:21 73:24 75:13 88:6 92:12,17 105:4 111:24 115:14 123:19 124:17 125:8 127:12 128:12 129:6,22 133:9 135:14 136:24 137:13 139:9 146:6 152:23 155:10 158:20 formal 114:8 formed 34:21 forms 113:2 forth 61:20,24 126:9 found 30:18 34:8 36:7 48:5 122:17 founded 34:6 36:5,14 37:3 founder 34:9 founders 37:3 four 108:13 139:18	frankly 19:13 79:22 freezes 131:10 frequency 133:6 135:12 139:8 frequent 133:6 134:21 frequently 65:21 93:19 110:11 134:17 fresh 130:9,13 fridge 75:1 127:22 128:2 friends 20:13 front 5:20 6:13 26:15 133:10 133:17 162:16 frozen 95:11,14 95:18 96:7,10 96:20,21 full 48:10 132:4 146:11 147:15 function 41:10 130:10 functional 36:17 37:2 functioning 36:12 37:4 funding 19:5 further 11:21 22:15 149:6,9 162:5	g gastroenterol... 47:21 ge 48:17 49:12 gender 67:15 gene 18:24 41:19 42:5 52:11,12 148:17,20 genealogy 19:2 geneoscopy 1:5 7:16 13:6 14:15 31:9 40:4 165:4 166:1 167:1 geneoscopy's 13:15,24 14:4 14:21 general 13:10 43:4 81:14 106:16 134:8 generally 23:6 44:7 125:9 getting 47:12 138:4 gfoht 120:24 122:3,13,19,23 122:24 124:3,7 125:14,23 126:16 158:8 158:10,12,19 160:12,13 161:15 162:20
--	--	--	--

162:22 163:1 gi 50:20,22 give 4:18 5:17 16:14 27:14 60:6 62:2,16 62:18 114:18 117:15 118:22 131:18,22 139:14 given 39:9 59:20 139:3 167:9 gives 114:19 117:18 giving 69:14 91:2 global 39:14 go 26:24 27:14 44:15 45:5 70:15,17 72:13 83:5 90:8,22 92:5 94:5,19 95:21 97:16 100:10 104:7 105:22 132:2 140:11 146:9 148:5 154:1 156:11,17 goal 61:4,7 88:13 goes 44:12 45:16 68:23 150:17,18	going 18:17 23:9,14,20 31:22 37:5 44:1,8 70:15 79:11 86:10 90:17,20 104:9 109:17,18 110:6,16 113:23 124:5 133:1 138:2,3 141:1 143:1 155:12 gold 46:15,22 47:8 50:12 58:12,16 68:2 68:7 good 4:4,5 10:23 20:14 49:1 51:21,22 59:15 69:3 78:10,19 79:12 85:24 86:2 90:19 98:21 104:5,6,10 106:18 109:5 111:6 139:14 140:19 145:5 google 136:5 googled 136:4 grad 37:20 grain 19:9 grants 19:4 greater 157:23	ground 4:12 group 38:21,24 39:6,11 groups 52:8,10 growing 60:22 60:23 106:9 guaiaac 96:2 120:13,14,17 122:3 guess 71:5 83:6 121:24 156:11 guidepoint 39:14	59:9 79:13 happens 113:15 127:15 hard 4:17,24 50:5 101:10 harder 78:17 hb 120:20 121:4 123:8 head 4:23,24 23:15 heading 80:14 health 34:2,3,6 34:11,16,18,23 34:24 35:20,24 37:8 heard 134:12 heart 79:1 helpful 127:24 heme 128:7 162:22,24 163:2 hemocult 158:1,14 hemoglobin 41:23 120:20 121:6 122:8,12 122:13,16 123:9,11 128:21 136:14 136:21 141:22 hereto 167:7 hic 98:20 100:7 116:11,14
		h	
		h 3:6 162:22 163:2 166:3 half 24:18 30:22 72:8,12 hand 90:8,8 93:17 95:21 123:23 124:5 127:3 142:22 146:12 164:8 handed 119:18 handling 50:6 74:15 hands 42:24 happen 130:19 happened 60:2 60:7 64:14 112:19,21 happening 57:15 58:24	

hic1 92:3,20 93:10,14,18 94:1 98:1,5,11 98:14,24 99:4 99:7,13,15 100:3,23 101:2 102:11,16 103:23 104:8 104:18 105:2,2 105:10,15,17 107:8,12,23 108:6,10,13,17 108:18,19 111:11,13,20 112:4,6 114:2 114:11,12,16 114:17,20,21 115:3,5,9,10,16 115:18 116:19 116:24 119:2 high 14:10 34:24 38:14 39:18 46:1 60:16 79:15 93:20 112:23 132:12 133:1,3 133:7,17,20 134:16,19,24 139:17,22 141:1,11 142:3 142:4,19 154:24 158:18 160:10	higher 45:22 60:19 71:18 72:24 75:9,19 77:9 101:1 107:24 116:3,3 118:8 119:10 150:13 151:11 152:13,13,20 152:21 159:16 159:22,24 160:3,17 highlighting 6:10 highly 51:16 61:10 98:7 99:1 102:22 125:19 hindsight 140:17 hired 21:8 historically 133:19 history 53:18 53:19 54:9 hoag 2:4 holding 36:13 36:16 holidays 24:14 home 124:22 129:21 144:9 157:5 honestly 105:17	hope 35:17 114:21 hopefully 23:21 104:9 hospital 97:6 hour 5:10,11 24:16,17,18,19 44:2 90:21 hours 25:11,12 25:13,24 27:16 28:15,16,18,24 29:1,8,10 39:12 95:3,9 97:1 157:6,23 huh 26:8 32:12 36:3 37:6 55:17 69:17 70:19 73:4 92:7 94:24 97:18 112:12 141:16 144:3,6 human 40:6,9 42:17,20,22,23 43:6,12 120:20 121:4 122:7,11 123:8 hypothetical 113:24 i i.e. 80:18 idea 41:4,7 48:7 61:3	ideally 133:11 134:4 identification 55:1,6 identified 49:16 identify 65:13 66:13,16 70:8 84:24 88:24 143:22 ideologically 106:8 ifobt 121:5,13 121:20 123:8 124:1 126:11 126:13 127:14 135:3 ii 158:1,14 illinois 1:17 164:4 imagine 78:10 109:3 immediate 131:15 immediately 19:16,18 129:19 157:18 immuno 48:19 immunochem... 3:15 119:23 121:4,11 impact 69:8 impactful 161:22
---	--	--	---

imperiale 3:11 21:21 53:7 54:11 55:12 69:15,20 70:23 77:19 81:1 112:9,19 implement 157:19 implemented 46:16,23 47:5 48:24 51:2 80:1 importance 88:2 important 18:20 59:4 60:9,20 63:20 65:6 68:6 69:11,11 76:15 78:16 88:1,5 89:14 90:4,15 102:2 113:1 115:19 137:7 150:18 151:1 152:14,17 importantly 65:18 78:2 101:5 impressive 78:6 impressively 78:2 improve 108:18 149:6	improved 3:17 102:11 143:5 147:5,21,23 improvement 15:24 57:23 107:20 111:21 150:2 improving 149:12,20 inaccurate 124:8,24 inadequately 124:9 125:1 inadvertently 23:22 include 72:5 85:12,13 104:21,22 107:19 140:17 included 30:16 30:17 41:12 162:13 includes 122:16 including 30:8 inconsistent 112:3 inconvenience 74:24 75:4 incorporates 79:4 incorrect 108:22 increase 57:3 77:22,23 78:6	78:20,21,22 100:22 102:13 102:19 103:19 109:13 115:23 147:13,14,24 149:21 increased 94:10,16 107:9 109:11 147:9 148:12 149:7 increases 125:20 increasing 149:13 independent 18:8 19:17 110:12 112:20 independently 84:20 indicate 88:17 indicating 59:20 indication 63:16 116:23 indistinguish... 116:20 individual 92:9 individuals 146:18 152:6 inexperienced 111:5 inflammatory 157:22	information 17:16,21 22:1 28:19 32:10 infringement 13:7,16 14:1 14:24 inherent 154:10,19 initial 11:2 151:6 innovation 17:20,23 19:19 20:2 inserted 48:1 institute 18:15 institution 32:24 instructed 157:1,19 instructions 4:10 insufflation 49:24 intent 126:19 133:21,22 inter 30:7 31:10 interest 47:14 51:5,6 interested 40:14 106:6 interpret 61:13 105:9
---	---	--	---

interpretation 95:16 136:1 interpreted 61:11 interrupted 131:21 interval 67:20 102:16 116:11 150:3 intervals 116:13,15 149:24 introduction 52:22 83:7 88:20 introductory 63:6,7 121:24 intuitive 89:13 90:10 intuitively 86:1 invalid 13:9 invariably 109:16,18 invasive 65:20 invented 53:14 invention 53:13 inventor 53:21 investigate 41:9 investigated 52:16 131:3,20 investigators 52:11 80:5 111:4,5 133:12	134:5 investment 49:11 involve 136:15 138:4 142:1 involved 157:10,15 158:19 160:11 involves 158:12 161:14 ipr 5:24 6:13 6:19 8:7,13 10:10,16 26:17 26:22 27:20 39:24 91:3 ipr2024-00459 1:7 irrelevant 113:9,17 isolation 41:13 41:13 issue 49:18 issues 128:1 italy 135:6,12 135:19 140:16 itzkowitz 3:19 143:5 144:8 146:3 147:20 153:2,6,13,20 154:7,16,19 155:3,4,13 156:6	j jama 14:5,10 january 1:18 13:3,23 16:3,6 17:13 22:7,8 22:12,15 33:22 164:9 165:3 japan 135:4,10 140:15 jobs 39:23 johnson 37:16 37:16,19,19 joint 80:20 jones 2:4 3:3 4:3 6:4 13:20 13:21 23:13 26:10 44:1,5 44:15,18 46:11 53:23 61:14 68:17 69:19 74:4 75:16 90:20 91:1,7 92:13,21 107:4 112:8 115:1 118:3 119:14 119:17 123:22 124:21 126:4 127:18 128:18 129:7,10 131:14 134:2 135:17 137:8 137:17 140:22 142:21 146:8	153:1 155:11 155:21 156:1,3 158:22 162:3,5 163:5 joost 20:11,24 32:6 53:24 journal 14:10 53:7 55:14 jumping 23:3
			k keep 79:11 127:21 kept 129:1,3,13 129:15 130:2 key 141:20 142:16 kind 7:1 15:22 18:16 20:3 67:12 74:20 76:8,12,13 80:2 88:21 101:19 106:7 106:10 109:23 kinds 12:18 kit 144:18 knew 21:15 know 5:13 8:10 11:12 15:8,22 16:19 18:1,2,9 18:18 19:3,16 20:1,6,16,18,24 21:2,3,6,10,10 21:16,17 33:20

35:11 39:2 49:14 53:13 54:10 56:15 57:22 58:1,11 66:19 67:23 68:22 79:22 86:20 97:11,12 102:18 105:23 106:5,15 113:8 118:14 knowledge 30:12 35:20 36:10 51:12 known 46:9 50:3,7,14 57:16,19 58:11 64:7 76:5 86:10,11 87:6 111:3 131:8 154:8,16	145:11,18 labs 43:9 125:11 lack 12:17 80:7 lacking 49:8,12 landscape 63:18 language 83:1 84:15,21 85:3 88:16,22 98:22 large 15:7 54:13 59:22 69:24 86:14 103:6 150:21 larger 151:9 late 68:19 launched 59:23 59:24 60:1 lead 21:21 44:24 45:14 52:13 leads 111:2 leaning 106:11 learn 18:12 led 40:24 112:22 113:8 left 37:5 93:17 124:5 127:3 132:5 146:12 legal 7:2,3 14:16 23:10 165:23 lehnard 91:8 91:18,22 92:5	96:2 119:1 162:13,16,19 length 16:24 17:3 lesion 66:24 67:2,21 lesions 50:16 60:23 66:12,15 66:20,21 71:24 72:5,9 75:10 75:21 78:16 84:7 85:24 86:2 134:22 level 34:24 38:14 39:18 41:8 123:12 license 164:14 licensed 54:7 lid 157:4 likely 102:22 115:12 135:24 136:8 151:4,7 limit 13:18 limitations 49:4 125:23 126:18 line 71:9 166:4 166:7,10,13,16 166:19 lines 29:11 58:9 59:13 61:12 75:4 list 29:15 38:22 101:21 104:3,3	108:10 listed 29:20,23 30:2 56:17 62:15,24 63:3 63:5,8 125:15 126:12 listing 63:13 123:16 literally 78:11 literature 29:24 30:1,19 52:7 litigation 6:22 7:17,22 8:3,21 9:22 10:15,17 11:3 12:4,10 12:17 22:10 33:15,23 little 12:24 72:12 129:9 131:9 150:9 157:14 living 131:13 llp 2:4,10 location 65:14 67:14 logically 85:22 85:22 long 24:15 25:10,21 37:20 38:2,4,8 longer 37:2,4 look 26:14 29:12 30:5
I			
I 20:10 40:21 lab 36:15 42:24 43:24 96:10 97:3 124:20 131:24 157:12 laboratory 95:4,8,12,19 124:15 125:5 128:4,11,16,17 128:19 129:3 129:15,19 144:22 145:2,6			

41:21 42:1,5 44:11 62:21 73:3 75:14 76:10 80:9 87:11,18 100:17 101:6 101:14 102:8 104:7 106:10 108:7,12 109:24 116:12 116:18 117:2,4 117:6,8 118:1 118:1,14 120:2 121:23 123:6 132:4 133:24 136:10 141:13 144:4 147:12 148:16 151:19 151:19 153:11 156:23 159:10 looked 6:8 17:10 52:8,9 52:11 158:7 looking 11:8 15:16 48:3 49:9 83:14 101:11 103:4 120:11 149:23 150:9 154:3 looks 97:2 120:11 135:9 156:20 lot 13:9,13 14:2 19:8 49:14,14	50:23 66:7 89:21 109:9 116:20 151:10 152:16 louwagie 20:11 20:16,24 53:24 54:1 louwagie's 32:6 low 44:21,22 50:10,17 78:10 82:19 120:19 122:4,7 125:15 lower 45:22 50:4,22 67:4 lumping 150:8 lunch 119:14 120:15 lymph 66:5 m m 2:9 162:22 163:2 165:1 ma 2:5 made 19:10 51:13 100:11 104:12 106:7 107:2 167:5 madison 2:10 main 49:6 major 47:11 52:1,1 65:21 75:23 77:13,22 78:21,21,22 79:10	make 23:15 29:4 62:4 85:16,16 86:4 90:17 100:17 101:10 102:24 103:22 104:2,2 104:15,16 108:22 118:11 118:21 124:11 136:10 142:13 142:18 144:12 150:4,7 152:7 makes 4:16 5:8 78:24 85:22,23 103:15 making 51:14 113:4 117:14 149:18 150:20 151:19 152:3 manipulation 146:4 157:15 158:19 160:11 161:15,18,20 161:23 162:2 manufacturer 157:20 marginal 78:4 78:23 140:4 marginally 102:18 103:9 mark 6:6 9:20 marked 6:2,3 69:18 91:6 119:16 142:20	155:20 marker 91:23 92:2,20 93:1 98:1,21 102:12 108:6,21,23 109:1,4,6,7,9 109:21 110:14 110:14,19,22 111:11 112:7 112:13 147:8 markers 14:9 17:19,23 18:22 21:19 52:15 93:12,13 98:6 98:24 99:8,15 99:16,21 100:7 101:22 104:4,8 104:18 105:24 106:11,15,16 106:18 110:1,7 110:12 111:2,6 112:3,21 113:2 131:7 145:21 151:10,11,15 152:2 marlborough 144:1 massachusetts 144:2 materials 28:10 29:16 94:19 mathematically 109:23,24
---	--	--	---

matter 6:23 9:18 11:6,14 11:22 22:17 33:16,24 38:15 39:4,18 52:2 65:7 79:1 mean 6:6 10:15 24:10 25:16 42:10 43:15 45:13 87:24 121:21 135:21 159:17 meaning 88:12 109:14 means 68:16 81:4,5,23 83:1 84:23,23 87:12 95:17 98:12 99:12 102:6,21 109:17 110:18 114:12 meant 38:7 measure 117:3 117:5,5 measuring 78:8 medicine 53:7 55:14 86:3 meeting 17:1,4 24:19 25:10,14 25:19,21 26:1 meetings 12:23 13:2,4 16:3,5 16:10,17,19 17:7,8,13 22:7	22:11,14,16 23:8,14,18 24:3,4,5,6,7,15 25:5,8 member 34:10 membrane 66:4 memory 10:23 mention 11:11 30:6,22 50:19 57:4,8 73:15 73:20 99:10,11 105:13,14 106:20 126:13 mentioned 9:2 9:13 15:5 16:2 21:23 32:22 35:24 57:17 63:21 64:10 100:23 101:7 110:9 152:19 mentioning 69:16 mentions 73:20 merit 1:15 met 9:15 10:3 metastasis 66:9 method 3:13 83:15 91:10 methods 94:19 147:5,21 methyated 145:24	methylation 3:12 52:15 91:9,23 92:2,3 92:8,16,20 93:1,5,10,19 94:1,15 96:16 96:22 98:6,24 99:7,15 100:7 103:18 104:4,7 104:17 105:24 106:10,14,22 106:22 108:10 148:17,20 149:2,7 metric 102:3 metrics 82:4 mid 139:24 middle 110:17 midst 18:16 mind 44:14 74:1 117:20 137:16 minor 147:16 minutes 17:2 25:11,12 misread 46:19 129:8 misreading 59:16 missed 115:11 mistake 22:9 mistaken 76:9 mix 15:11	modified 28:12 molecular 18:22 41:14 67:14 moment 44:16 monday 25:9 months 9:8,9 morning 4:4,5 morningside 37:23 38:10 mortality 45:21 45:22 mounted 157:3 mrna 41:20 mucus 41:8,8 multi 70:24 73:9 81:20 83:12,22 146:15 153:15 155:6 multicenter 15:10 155:15 multiple 60:18 78:14 80:3,3 95:18 151:10 155:23 mutations 18:24 41:19 52:12,12 106:6 n n 1:17 2:1 3:1 name 20:8,9,13 53:21 117:17
---	--	--	---

names 16:11,14 70:11,12,14 143:15,19 nanocytomics 34:20,21 36:2 36:7,11,19 37:5,8 national 18:14 nature 40:13 nci 19:4 necessarily 17:9 48:9 66:5 125:19 138:10 138:14 139:6 necessary 167:6 need 5:11 16:15 20:14 35:7,11 48:8 60:23 82:10,17 84:17 84:19 87:12 88:24 101:13 105:22 106:1 106:18 111:9 116:6 123:10 127:21 129:20 154:8,16 needs 50:12 149:16 negative 74:3 92:20 93:9,12 93:14 118:15 negatively 130:16	negatives 15:6 neoplasia 77:1 122:5 network 18:14 never 10:3 98:15 108:20 117:2,4 new 2:11 34:21 53:6 55:14 106:9 154:22 nma 14:9 nodding 4:23 nodes 66:5 nomenclature 85:3 88:8 non 120:19 122:7,11 nonobvious 14:16 nonsteroidal 157:22 nonverbal 5:1 normal 85:14 133:7 134:17 northwestern 18:5 notary 167:13 167:19 note 93:17,18 165:10 noted 167:7 notes 6:10 novel 3:13 91:10	november 10:21,22 11:15 11:17,18 22:11 nuance 88:7 89:7 nucleic 17:18 17:23 18:23 19:11 21:19 54:21 106:15 112:22 113:10 113:12,19 145:20 number 27:15 31:1,11 44:23 54:15 82:7,16 88:23 89:5 118:6,11,19 119:9 136:12 136:20 137:19 139:13,23 140:10,12,20 140:21,24 141:15,18,23 142:6,11,13 150:21 numbers 11:13 50:10 55:18 56:17 57:5 81:13 86:22 87:5 103:1 ny 2:11 165:15	o o 35:3 object 4:19 objection 46:4 53:16 58:21 68:12 73:24 75:13 88:6 92:12,17 105:4 111:24 112:16 115:14 123:19 124:17 125:8 127:12 128:12 129:6,22 133:9 135:14 136:24 137:13 139:9 146:6 152:23 155:10 158:20 objectives 120:12 observed 155:4 155:13 obtained 136:13 137:19 obviously 14:11 21:19 117:20 obviousness 59:10 occult 3:15 18:22 19:11 48:18,20 56:24 95:22 96:1,3,6 96:12 119:23
---	--	--	--

120:13,14,17 122:3 132:12 153:16 155:7 155:16 162:19 occurred 54:18 october 33:1,14 33:19 offered 55:7 office 1:1 oh 30:11 40:18 75:17 147:1 okay 4:10,22 8:22 10:13 20:12,14 22:6 23:3 25:1 26:14 27:17 33:18,20 38:20 41:7 44:10,19 54:4 62:6 69:4 69:14 72:17 73:7 75:18 80:9,12 83:10 83:16,16,18,21 90:20 109:2 126:5 132:8 134:9,14 144:17 154:13 155:12 156:1 older 29:24 once 27:23 123:16 128:10 135:22 136:6 149:12 154:6 158:1	oncomethylo... 20:20 21:14 ones 48:23 51:8 66:21 124:2 ongoing 32:8 32:13 onsite 35:4,9,16 operator 15:18 76:6 opinion 19:9,24 20:5 64:23,23 74:14 opinions 32:11 61:16,20,24 opposed 35:9 152:16 optimal 136:13 136:21 139:13 140:10 149:1 optimally 148:8,9 optimize 109:13 optimized 77:18 119:5 option 100:8 105:15,20 options 161:9 orally 4:23 oranges 112:18 order 50:13 82:1,10 112:4 114:5 116:7 133:23 138:24	organ 66:10 organism 131:13 original 152:4 originally 50:20 originated 36:1 outcome 80:16 80:24 81:3,5,5 83:3,4 84:16 87:21 115:12 outcomes 80:14 outside 7:4 150:2,3 overall 57:2 79:3 103:3 160:3,17 overfit 151:5 overkill 139:19 overlap 116:16 overpowered 81:10 own 67:7 90:5 100:17 owner 1:9 2:8 owner's 6:15 owners 70:17 ownership 21:4 p p 2:1,1 p.m. 163:7 page 3:2,6 26:24 27:1,23	30:21 31:8 32:23 44:6,12 46:14 51:9 62:22 70:15,17 71:3 80:9 83:5 83:19 91:14 92:6 93:16 94:5,20 95:21 97:16,16,17 126:21 132:2 142:24 144:4 146:9 156:11 156:12,12,17 156:18 162:20 166:4,7,10,13 166:16,19 pages 70:16 painful 49:23 pairing 158:10 panel 41:18 76:24 77:1,1 127:3 146:15 147:9,15 paper 3:11,19 14:4 15:2,4,22 57:13 58:22 59:4,7,14,21 69:20,21,24 70:7,23 76:8 77:19 79:13 81:1 83:5 89:22 90:11 91:2,8,18,18,22 94:5,20 97:17
--	---	--	---

99:3,19,24 100:1,13 102:24 104:11 104:14 106:2 113:24 119:20 120:5,6,10 121:23 123:7 123:17 124:2 125:24 127:13 129:23 130:7 130:20 133:4 133:16 139:11 140:18 142:15 142:22 143:2,4 143:8,12 144:4 153:6,21 156:5 156:8,14,20 159:8 papers 100:16 paragraph 29:13,15,20 30:2,4,6,21,22 32:5 44:11,19 44:21 46:12,13 46:21 52:20 54:23 55:3 56:10 57:5,11 58:2,18 59:14 60:3,5 61:6,8 61:11 63:7,10 63:22 69:21 80:13,15 83:6 83:17,18 84:23 88:20 91:13,20	94:7,21 95:2 97:21 98:10 99:23 118:21 120:2,7 123:6 124:6 125:13 126:1,3,6,10,19 128:24 132:4 135:1 136:11 141:9,14 143:1 143:10 146:11 147:20 153:11 153:13 154:1,3 154:9 paragraphs 126:7,8 parenthesis 160:19,20 part 8:5 14:5,6 14:6 18:9,9 43:15 60:14 96:14,19,20,21 97:10,10 112:14 127:14 127:15 130:6 138:1,6 142:9 150:6,7 partes 30:7 31:10 participants 86:24 participating 158:2 particular 39:4 57:5,12 58:8	59:4,13 60:20 61:2 77:4 101:9 119:4 126:13 134:19 137:3 161:22 particularly 127:23 parts 56:10 past 101:7 patent 1:1,2,8,9 2:8 6:15 7:9,12 7:15 13:7,8 14:15 17:6,9 17:12,14,18 18:7 19:15 20:3 21:4,5,8 21:24 31:11,11 31:14,17,17 32:2,3,3,7,8,9 32:13,14 53:14 53:18,19,21 54:5,7,9 59:10 70:16 patent's 31:19 patents 11:13 19:14 31:18 32:1,16,18 patient 35:12 45:9,16 46:18 47:1 48:5 68:9 68:14 74:12,12 86:10 101:22 108:15 117:17 125:17 131:5	144:9 146:4 154:8,11,17,20 154:24 156:20 patient's 45:17 129:21 patients 15:8 15:11 45:21 47:11 48:8,9 48:11 49:6,19 49:22 50:6 51:13 54:15 66:8 72:8 74:17,22 81:21 82:20 84:19 86:9,15,18,19 86:20 87:15 88:24 89:2,5 92:9,19,22 93:8,9,14,21 97:3 108:9,13 108:16 115:3,8 115:11 116:7 118:15 131:4,5 133:20 134:20 134:23,24 140:6 153:10 154:22 160:4 160:12,18 patterson 8:24 9:15,17 patterson's 8:15,18 pause 44:13
--	--	--	--

pcps 49:6	146:21 147:2,3	112:24 117:8	113:18 139:15
pending 5:14	147:9,10,17,17	119:21 140:5	pertinent 59:8
penetrated	147:24 148:2	148:13 151:7	petition 30:6
66:3,4	148:12,22,22	151:17	30:10,11 31:9
people 16:16	149:3,3,8,10	performed	32:7
19:2,8,21	150:3 152:5,10	124:20 135:6	petitioner 1:6
57:19 64:23	159:12 160:5,5	135:19 144:8	2:3
65:6,6 70:14	160:6,7,19,20	151:24	physician
74:21 76:6	160:21,22,24	performing	47:23
84:21 85:24	161:1,3,4	108:6,21,23	pick 42:15
88:9 100:1	percentage	109:1,4,5,21	86:12
143:13 150:24	160:4,17,19	110:14,19	picked 117:15
perceived	percentile	111:11 112:13	picks 117:16
125:13 159:23	50:17 56:22	145:14	picture 145:9
percent 55:15	139:24	performs 103:9	piece 64:16
55:16 56:2,3	perception	103:11 108:24	place 12:6 13:2
56:19,20 57:1	156:20	109:2,4,7	24:8 63:4,8
57:22,22 67:5	perform 110:15	110:1,22 114:3	placed 128:2
67:6,16,17,18	110:18 116:24	114:11 130:9	places 62:5
67:22 71:7,7	124:15 125:11	period 38:2	89:21 121:15
71:10,11,24	145:10 151:20	43:11	planning 54:16
72:1,11,19,19	performance	periodically	plastic 157:2
77:21,21,24	3:14 50:8	14:7 39:1,16	please 4:22 5:5
78:1,9,14	52:14,18 61:15	43:15	5:13 41:6
81:15,16,17	61:19 63:11	person 24:6	plus 24:12,13
82:19 86:16,20	64:2,3,4,6,13	25:6 118:1	30:4 49:18
86:24 87:2,3	76:3,4,14 77:7	person's 73:8	105:10,15,18
102:14,14,15	79:3 82:3 84:1	personnel	114:11 115:17
116:9,10,10,15	84:6,10 90:6	124:9,15 125:2	149:2
117:19 118:5	100:4 103:3,6	125:6,10	point 57:19
118:17,18	107:12,15,16	perspective	60:2,3,4 63:10
119:3,7,8,10	107:18,22	15:7,20 17:17	63:21,23 64:7
139:21 140:1	110:3,4,16	17:19 75:3	64:12 65:6
146:15,16,20	111:2,8 112:23	77:11,12 89:8	68:6 69:5

76:19 77:16,19 102:15 112:6 114:20 116:10 134:23 160:15 pointed 63:5 128:23 pointing 63:19 points 41:11 polyps 49:16 49:17 60:17 66:14 78:7,23 122:6 population 81:14,24 87:7 87:10 118:13 118:15 132:13 133:2,3,14,15 134:8,10 135:3 136:15 139:3 141:2,11,19,24 142:4,15,19 populations 133:7,8 134:16 134:18 137:12 138:9,14 portion 96:10 96:15 127:10 128:21 portions 95:18 positive 15:9 73:12 92:19 93:9,13,15 109:15,15 117:17	positives 15:5 44:24 108:14 109:17 possibility 124:8 130:8 possible 126:15 151:16 possibly 140:1 potential 11:6 11:22 12:22 13:7,16,24 104:4 150:21 151:3 potentially 10:14 32:18 power 82:1,2 82:14,21,22 84:17,24 87:8 87:22 powered 81:7,9 82:11 powering 88:18 practical 90:18 practically 50:13 52:17,17 66:19 practice 11:9 20:14 49:7 57:20 80:1 114:6 138:16 practiced 48:22 125:23 practitioners 151:14	pre 65:1 158:3 precancerous 66:12,14,20 71:23 72:5,9 75:10,20 84:7 precede 66:17 precisely 75:24 110:22 131:12 prediction 104:10 150:22 151:4,5,12 predominant 18:24 predominantly 133:19 prefer 151:15 161:2,10 preference 160:7 preferred 153:16 155:6 155:15 160:4 160:13,18,23 161:1,4 preliminary 6:15 36:15 40:24 154:21 prep 49:20 159:17,22 prepaid 158:3 preparation 23:3,9,12 26:4 49:20 94:22 97:4 159:3	prepare 23:6 23:24 24:1 35:2,7 preparing 27:13 28:9,17 28:22 29:6,16 29:22 31:14 158:12 prescreening 68:3 present 25:14 42:2 132:6,9 preserve 43:20 preserved 148:8,10 presumably 74:23 presume 8:4 41:23 132:23 pretest 50:14 pretty 24:17 80:6 89:20,21 97:9 104:9 105:11 prevailing 19:9 19:24 prevalence 67:22 81:13,15 82:19 86:16 87:2,6 prevalent 81:9 82:13,15,24 84:24 87:19,23
--	---	--	---

prevent 35:11 previous 16:2 31:8 153:15 155:5,14 previously 37:18 primarily 12:15,18 14:17 23:9 51:20 52:3 61:8 primary 47:21 47:22,23 53:20 64:24 80:14,16 80:24 81:3,5,5 83:2,24 84:9 84:17 87:16,17 87:20,21,21,23 prior 11:22 13:11,22 19:14 22:4,17 30:1 30:13 31:4,14 32:14 45:14 47:7 50:15 51:24 54:18,22 57:15,16 58:24 59:9 64:24 priority 20:6 privilege 23:23 prize 74:21 probability 115:17 probably 18:1 27:16 38:6 43:14 64:16	68:20 83:14 88:4 97:6 100:9 102:21 probe 47:18,24 127:7,16 problem 49:2 problems 47:11 50:3,24 51:3 126:2,9,12 procedure 35:3 35:5,9,12 47:10 65:12,16 65:16 74:20 85:14,15 127:15 proceeding 6:20 7:5,9 8:7 10:10,16 26:17 26:22 27:21 39:24 proceedings 164:5,7 process 42:23 74:7,9 146:3 157:15 processed 35:15 processing 40:6 40:9 41:13 158:3 product 111:18 professional 124:15,20 125:5,11	professionals 67:24 profile 14:10 65:24 progression 40:15 41:10 67:1,4,13,16,17 67:19 projection 87:8 prominently 57:6 promising 52:6 99:17,21 100:9 103:16,24 105:10,18,21 105:24 106:14 146:13 promoter 3:12 91:9 promotor 93:19 pronounce 20:8,13 53:22 proof 110:23 116:5,21,22 properly 113:5 propose 117:21 proposes 110:24 prosecution 32:8,14 prospective 82:14 86:8	protein 41:21 41:24 92:9,14 162:13,24 163:2 proteins 41:24 42:1,2 52:4 55:1,6 91:24 protocol 97:2 97:14 prototype 146:14 148:11 152:4 prove 86:3,5 111:9 provide 46:17 47:1 52:17 55:18 56:12 61:8 74:10,11 74:14 75:6,7 101:18,19 140:18 provided 15:17 148:21 provides 92:8 116:4 129:24 providing 123:24 psychological 35:2,4 public 167:19 publication 54:11 publications 19:3
---	--	--	--

publicly 43:8 published 14:5 21:21 53:6 55:13 57:13 59:23 purified 148:8 148:10 put 6:12 20:3 58:2 75:1 79:12 106:2 127:11,17 128:14 143:3 156:4 putting 155:22	43:3 62:14,16 64:12 66:21 74:2,5,19 75:14,15 89:11 93:4 107:15 109:6 113:18 114:6 115:23 123:21 124:23 128:13 133:18 133:24 137:15 137:23 139:5 153:5 162:11 questions 11:24 12:1,3,6,11,18 143:1 162:5,8 163:4,5	r r 2:1 35:3 166:3 166:3 radiation 65:22 65:23 66:8 radiological 48:13,14 radiologically 66:6 random 78:12 range 82:6 rapid 35:4 rapidly 106:9 rate 67:4,13 94:10 159:13 rated 159:24 rates 94:17 rather 4:23 ratings 159:17 159:22 reach 50:1 read 9:6,9,10 9:11,24 10:6 15:21 27:9 28:5 58:9 59:12 61:10,12 62:12 90:11 98:19 99:24 100:1,12,15,16 129:11 146:22 154:13 155:12 165:9 167:5	reader 102:24 reading 99:18 120:16 real 106:16 realistically 137:4 really 4:17 13:13 19:14 32:17 35:22 49:2,20 50:1 51:4 65:11 74:14 90:8 106:18 116:8 116:20 130:5 130:21 134:22 139:20 142:13 143:16,17 161:22 realtime 1:16 reanalyzed 101:23 reason 5:11,17 35:23 58:8,9 60:19 62:1 63:19 64:9 76:15 88:21,21 99:23 105:11 116:17 130:6 165:11 166:6,9 166:12,15,18 166:21 reasonable 15:12 66:18,19 67:22
q	163:4,5 quick 65:4 162:8 quickly 35:7,15 97:1 quinn 2:10 16:17 quinnemanue... 2:12 165:2 quite 15:11,19 21:17 54:21 90:17 151:20 151:24 quote 90:13 140:16 153:13 155:3		
qualified 149:16 qualify 34:9 115:19 quantification 121:6 123:11 quantitated 123:8 124:1 quantitative 3:15 119:23 121:11 126:14 quantitatively 161:18 162:1 question 4:15 5:4,7,14,15 14:23 23:21 26:7 29:4 31:22 32:21			

reasonably 98:21 reasons 18:1 49:7 100:2,21 107:2 recall 9:5 10:9 12:19 13:9 14:2 16:5,9,16 16:24 17:3 21:7 22:19 24:22 27:12 28:8 29:10 33:13 38:11,12 162:14 receipt 165:17 receive 96:18 134:20 received 11:4 12:24 95:2,8 95:12 96:9 159:16 receiver 15:18 76:5 receives 159:22 recent 43:17 recognize 26:20 27:19 70:6,11,13 91:4,8 119:20 143:4,12,15,18 156:5 recognized 19:16,18 154:7 154:16	recollection 33:9 recommend 61:10,12 134:24 recommended 48:6 134:16,20 159:3 recommending 68:2 record 5:1 44:15,17 90:22 164:7 recorded 27:15 55:13 134:9 records 16:15 27:14 recruit 81:21 81:23 82:17,20 84:19 86:8,18 86:19 89:1,6 116:7 recruited 54:15 86:24 recruiting 38:16 recruitment 54:16 rectum 48:2 recurrence 66:9 refer 43:5 51:8 51:17 77:6 143:8	reference 56:17 56:18 57:7,17 64:7,8 80:10 80:11 122:12 141:11,17 referenced 165:6 references 29:24 30:4,9 30:11,13,14,15 referencing 59:14 referred 30:13 33:6 referring 7:24 43:7 44:7,8 47:5,6 51:19 59:21 64:1 71:1,13 79:20 79:22 84:14 114:7 138:20 138:21 refers 70:24 89:11 122:11 124:24 126:24 142:2 148:6 refrigerate 74:22 refrigerated 129:21 refrigerating 130:15 refrigeration 130:9,22 131:6	131:9,10,16 refrigerator 129:2,14 regarding 22:2 153:3,7 regardless 130:24 regards 138:5 regimen 45:8 45:12 140:14 registered 1:15 regress 67:6 regulatory 85:8 114:9,15 related 11:9 12:16 13:11 14:4 131:18 159:18,23 relationship 7:5 35:21 36:24 37:7,12 relatively 147:16 148:1 158:18 released 53:2 53:10 relevant 30:19 32:10 52:9 58:23 61:20,23 66:13 106:8 rely 61:15 remained 52:21 53:4
---	--	--	--

remaining 96:14,15 remember 13:13 14:12 15:21 16:11,12 16:14 17:21 18:18 19:6,6 19:12 36:8 38:18 103:14 106:4 remind 29:3 remove 66:14 66:16 removed 60:24 65:14 96:11 127:11,16 repeat 35:12 93:4 123:20 142:8,17 145:8 153:5 repeated 58:14 132:12 repeating 137:16 rephrase 75:18 rephrasing 74:1 report 90:1,6 103:1 153:2,6 reported 59:7 102:12 164:5 reporter 1:16 1:16 4:17 5:1 164:4,14	reporting 147:20 represent 136:4 require 122:19 required 74:16 74:21,22 75:2 130:1 138:24 167:13 requirement 82:22 123:3 requires 146:3 158:10 161:17 161:18 research 14:7 18:3,8,10,14 36:14 43:16 51:5 88:11 111:15 reserved 163:6 respectively 72:20 119:3 148:22 respond 11:18 response 6:16 8:15,18 35:18 159:12 responses 5:1 responsible 18:15 restate 74:5 restriction 122:20,23 123:3	restrictions 121:5 123:10 125:15 157:20 result 45:17 86:23 116:6 119:5 131:11 150:1 resulted 94:10 94:16 149:2 results 15:15 44:22,23 53:8 71:4 73:12 86:6 89:24 92:9 101:8 118:16 131:12 139:16 146:14 148:5 149:19 153:3,7,14 155:14 159:10 160:16 retained 10:9 retaining 10:18 return 165:13 165:16 returned 129:2 129:14 158:2 reveal 23:11,23 revealing 23:4 review 8:23 17:10 26:4,11 30:7 31:4,7,10 32:7 153:23,24 165:7	reviewed 7:21 8:1,5,6,10,13 8:14,17 9:2 23:19 29:16 30:6,16 31:14 31:19 32:1,19 32:23 33:17,21 reviewing 33:9 33:13 richard 1:15 164:3,13 right 5:22 7:19 8:12 9:3 10:7 10:21 13:20 24:14,20 26:22 28:18 31:15 33:11 34:6 35:9,16 36:17 38:12 45:6,18 46:5 47:3,4 52:24 53:2,11 54:4 55:17,20 55:21 61:21 62:7,21 68:11 69:22 71:8,16 72:21 73:1 81:2 83:10,15 84:8,12 88:14 89:19 91:15,20 91:24 92:10,23 93:7,8 94:7,12 94:17,24 95:5 95:6,9,10,12,15 95:21,24 96:7
--	--	---	--

96:12,17 97:9	158:8,15,16,24	rules 4:12	137:11,19,23
98:21 102:14	159:5,6,8,20	run 114:21	138:15 139:16
105:5 107:6	160:2,9,23,24	running 137:12	139:18,20
108:11 109:16	160:24 161:6	s	140:3,24
110:4 111:14	161:11 162:15	s 2:1 3:6 35:3	141:15,24
111:23 112:11	162:22	166:3	157:5
113:2,11	rise 21:5,8	sample 35:7,10	sampling
115:13 117:20	risk 36:15 73:9	41:13 74:7,8	126:22 127:4,5
118:5,7,9,10,12	132:12 133:1,3	96:11,15,18	128:24 129:3
120:7 121:1,2	133:7,17,20	127:10,16	139:7
121:11,18	134:16,18,19	128:4,14	satisfaction
122:14,24	134:24 135:3	129:18 130:15	154:24
123:6,14,18,23	136:15 141:1	130:17 144:5,9	satisfy 82:22
124:3,11,12	141:11,19,24	144:18,21	saw 19:15,16
125:2,3 126:11	142:3,4,7,15,19	145:7,11,16,21	20:3
127:7,19 128:5	146:17 152:6	samples 35:3	saying 7:13
129:5,17 132:3	robust 55:8	40:7,10,14	71:12 98:22
132:18,21	60:16 81:19	41:3,9,17,22	104:6 130:18
133:2 135:20	114:14	42:3,6,8,12,15	130:19 132:24
137:12,21	roc 15:18 76:6	42:17,21,23,24	136:19 137:10
138:17 139:3,8	76:7 77:1,2,16	43:2,6,13,20	137:18,22
140:21 141:2,3	79:2 90:7	74:13,13,23	138:8,9,13,23
141:6,18,19,21	101:16 110:5	91:23 92:15	139:5 142:3,16
142:5 143:20	role 40:16	93:2,6,20	150:11
143:24 144:12	rose 35:3	94:21 95:2,8	says 47:8 70:16
144:14,19,20	roughly 48:3	95:11,14,17	71:5,22 72:18
145:3,12,19	round 38:20,23	96:5,9 97:1,4,8	73:5,8 80:16
146:10,21	39:5,10	97:11 127:22	83:11,24 84:4
147:4,10,11,19	route 105:22	128:1,15,20,24	84:4 95:1,2
148:3,18,19,23	routine 160:6	129:12 130:2,9	97:24 98:4,20
149:4,10,11,14	routinely 135:4	130:10,12,19	98:23 118:20
152:6,10,22	rule 4:14,22	131:1,5,13,23	120:17 122:2
154:5,9,12	130:7,8 150:22	136:13,20	123:7 124:7
156:9,21 158:6	151:4,5,12		128:24 129:12

129:17 132:9 136:9,11 146:13 147:14 153:14 157:17 159:11 160:3 160:17 sb 159:16,21 160:4,18 scan 48:16 scenario 113:24 scenarios 114:23 scheduled 94:23 school 37:20 schroy 3:19 153:21,23,24 156:5 161:16 161:23 science 32:8 sciences 1:8 7:6 11:11 16:20,23 19:10 21:1,3,9 21:16 22:2 30:23 31:10 35:21 37:9,10 37:13 40:1 51:10 52:23 53:11,15 54:6 54:7,19 55:4 70:7,10,12,13 70:14,21 143:14,16,23	156:15 165:4 166:1 167:1 scientific 14:18 15:6,20 77:11 scientifically 14:8 scientist 79:6 scoping 48:7 scratch 10:13 107:10 109:2 138:11 154:6 158:11 screen 18:19 47:15 50:15 65:10 140:15 154:10 screening 3:15 3:18 11:10 18:3 45:8,12 46:15,23 47:9 58:12,16 63:18 65:1,10 68:8 83:13,23 98:3 119:24 120:18 136:14 143:6 154:20 160:6 se 14:24 sea 70:4 sealable 127:11 144:10 sealed 127:19 127:24 128:3,7 128:10,10 145:1,4 157:4	sealing 157:11 seaport 2:5 search 30:20 seat 157:4 second 4:22 5:23 17:4 25:19 27:20 28:9,11,14,20 29:12,22 30:21 44:8,19 71:5 92:6 94:8,20 98:19,23 103:1 109:8,12 116:17 146:12 150:7 152:14 152:15 156:12 156:17,24 secondary 61:16 62:22 63:24 64:21 80:14 81:11 83:3 84:5,5 85:2 88:1 89:18 section 62:21 62:23 63:1,24 64:20 71:4 73:5 83:7,15 86:23 91:19 94:19 95:22 97:19,24 120:6 120:12 121:24 126:22 127:1 143:9,20 144:5	148:6 159:10 see 6:11,17 26:18 29:14,15 29:18,19,24 31:2,3,12 33:3 45:2 55:10,11 62:7,11,12 63:10 66:6 70:20,22 72:2 72:3,14,17,22 73:13,14 76:23 80:13,15,22,23 84:3,8 86:21 89:20,23,23,24 90:2 91:17 92:7 93:22,23 94:4,7,13,18 97:19,23 98:9 100:8,19 102:9 103:8 107:20 107:21 108:12 110:11 114:3 114:17 116:19 117:10 118:20 120:8,21,22 121:8 122:9,10 123:15 124:10 126:21 127:1,8 132:14 135:7,8 136:17,18 141:18 143:7 144:6 146:19 147:1,4,18,19 148:14,15
--	--	---	--

149:21 153:18 153:19 155:1,2 155:9,18,19 156:13,16 157:7 158:5 159:14,19 160:1,8 seem 52:16 99:17,21 149:24 seemed 15:19 seems 136:6 149:24 seen 14:3,4 selection 121:6 123:11 send 35:10 sense 5:8 85:22 85:23 88:13 89:13,19 98:13 98:14 106:7 134:15 sensitive 15:14 49:8 56:18 71:15 79:4 98:1,6,7 99:1 sensitivities 76:20 77:17 80:2 sensitivity 44:21 46:1,6 49:12,18 50:1 50:18,24 51:23 55:7,8,15,18	56:1,8,13,23 57:8,20 58:3,4 58:19 60:11,13 60:16 62:2,8 62:16,18 63:2 63:4 66:18 69:10 71:6,19 71:23 75:19 76:1,17,18 77:22,23 78:3 78:7,9,12,13,20 79:16 82:3 87:9 100:23 101:7,12 102:13,16 103:4 104:5,17 107:17,19,24 109:14 110:5 115:24 116:9 116:11,13,14 116:24 117:3,9 117:19 118:2 118:22 119:2,5 119:6 120:19 122:4 125:16 138:5 139:15 139:17,19,21 140:2 146:16 147:3,8,14,24 148:11,21 149:3,8,13,22 150:12,13,19 151:8,22 152:14,20,21	153:3,7 sent 11:15 17:8 128:11,15,17 129:19 165:14 sentence 30:5 32:5 44:20 51:18 52:20 71:5,22 72:14 72:15 73:3,4,6 73:8,15,19 80:16 81:4 94:8 95:1,7 98:4,19,20,23 99:9,12 121:3 122:2 123:23 124:6,6,24 128:23 129:12 131:19,22 135:1,13 137:18 141:12 141:13 144:12 146:12,20,21 146:22 147:13 148:6 154:12 154:13,15 157:1,18 160:3 160:16 sentences 135:16 147:12 separate 131:4 149:18 separated 102:4	sequencing 43:8 serious 76:20 serrated 60:17 78:7,22 serve 34:12 37:22 38:20 39:5,13 served 6:19,22 7:1 18:13 38:1 service 157:6 services 10:17 11:3 serving 10:14 sessile 60:17 78:7,22,22 set 61:20,24 164:8 sets 126:9 setting 47:22 97:6,7 setup 39:15 seven 25:23 several 8:12 9:9 23:8 30:15 46:7 47:15,16 58:14 59:19 60:18 67:16 69:7 70:6,11 70:12,13 100:2 100:21 104:3 sfrp2 104:4 shaking 4:24
--	--	--	---

sheet 165:11 shipped 131:23 144:21 145:1 157:5 shipping 128:4 157:11 short 44:2 shorthand 164:3,14 show 76:10 85:9,10,18,19 85:21 86:6 88:14 89:14,15 90:7 93:18 115:16 119:1 139:17 showed 105:21 146:15 147:2 shown 49:2 131:16 shows 65:10 93:5,11 97:24 113:7,16 114:17 side 155:24 sigmoid 48:1 sigmoidoscopy 47:17,24 49:5 sign 165:12 signature 27:1 27:24 163:6 164:12 signed 10:12 22:24 165:19	significance 66:23 115:22 116:5 significant 17:20,23 19:19 19:20 20:2 21:20 47:14 49:3,11 51:3,5 54:13,14 57:2 57:23 59:2 60:8 66:22,24 67:8,13,21 101:3 102:19 102:23 116:2 117:11 119:11 122:5 134:22 137:2 149:21 150:1 151:22 152:12,19 161:19 significantly 45:22 68:23 73:10 77:9 79:5 82:4 116:3,16 131:11 140:5 signing 27:10 28:6 similar 15:19 39:15,20 43:14 47:19 74:17 75:5 142:8,17 142:18	simple 54:4 simplifies 106:23 single 110:9,21 116:10 117:3,4 117:5,16 157:2 situation 52:21 53:4 80:7 sizable 77:24 78:20 size 102:4,10 102:20 110:10 110:10,13 116:18 sizes 90:3 slide 125:19 slow 130:15 small 57:1 77:20 101:19 148:1,2 149:22 150:14 smaller 67:3 smear 125:18 smearing 158:11 smears 157:24 158:13 solution 51:16 solutions 60:6 165:23 somewhat 19:7 65:8 74:17 75:4 149:16 152:2	soon 65:24 82:20 sorry 10:13 22:9 42:10 43:3 46:19 55:2 73:5 79:10 83:15 93:4 107:9 120:13 126:6 127:5 131:21 131:21 138:10 145:8 148:9 154:6 161:1 sort 82:9 85:7 114:10 115:17 sounds 118:6 source 42:8,11 speak 111:4 speaking 4:16 44:7 specializing 10:18 specific 32:22 42:2 52:9 76:19 98:1,6,7 99:1 104:17 121:5 123:9,9 138:21 specifically 51:19 64:13 86:10 94:14 101:15 107:17 120:10 133:16 140:23 145:4
--	---	---	--

specificities 72:14,15,18 76:21 77:17 80:2 151:23	147:17 148:3 148:21 149:4,9 149:14,22 150:15,19 151:8 152:5,10	stages 45:24 staging 80:20 stakeholders 34:12 stand 112:7 standard 46:15 46:22 47:8 50:12 58:12,16 68:3,8 85:14 122:2 standards 23:10 54:14 start 120:10,16 138:11,12 started 18:4 25:22 40:12 41:1,2 42:14 starting 41:18 43:14 46:13,20 120:7 142:24 143:9 starts 20:9 72:14,15 83:8 94:21 132:6 136:12 147:13 state 94:9 164:4 stated 62:4,9 99:6 statement 86:4 88:2,2 107:14 108:2 115:20 117:13 130:1	statements 149:18 states 1:1 120:13 121:3 135:4,11 140:16 154:19 statistic 77:4,5 102:3 110:9 statistical 82:2 115:21 116:5 statistically 82:4 108:22 116:1 150:1 152:13,20,21 statistics 88:3 101:6,14 110:6 133:17 134:1 149:23 status 36:11 stay 109:7 staying 110:21 steering 18:14 stenographic... 164:5 step 22:6 55:2 65:4 75:2 99:14 100:6 130:23 stepping 34:23 stool 3:12 41:8 50:6 52:13 55:1,6 70:24 73:10 74:16 75:1 83:12,23
specificity 15:15 44:23 46:9 49:8,12 50:2 51:1,23 55:7,9,16,19,23 56:2,9,13,21 57:2,9,21 58:3 58:4,19 60:12 60:13,15,16 62:3,8,17,19,24 63:2,4 66:20 69:11 72:24 75:9 76:1,17 76:18 77:20 78:5,23 79:4 79:17 82:3 87:9 93:20 101:3,8,12 103:4,7 104:6 107:19 109:18 110:5 117:4,9 117:9,12,22 118:4,8,10,12 118:17,23 119:2,6,8 120:19 122:7,7 122:11 138:6 139:15,17,19 139:22 140:2 146:16 147:3	specifics 11:7 14:3 specified 157:20 specifying 75:17 specimen 147:6 spelled 136:5 spend 34:15 36:18 39:10 spent 27:12 28:9,17,18,22 29:6 spinoff 34:7 splitting 131:4 spoken 9:17 spot 67:12 spread 102:7 spun 34:19 35:24 ssp 61:2 stabilization 154:23 stabilizing 128:8 144:19 147:6,21 stage 45:20 55:8 68:20 80:19 86:2		

91:10,22 93:20 94:21 97:4 98:2,8 125:18 127:7,16 144:17 146:2 147:7 148:10 154:23 157:2 157:24 158:13 storage 127:7 stored 95:4 strong 116:21 116:22 structural 41:14 studied 141:23 studies 36:15 74:21 85:4 161:21 study 15:7,9,10 40:22,24 41:7 42:14,18 53:6 54:15,16,17 69:15,24 70:3 70:4,20 81:18 81:19,20 82:1 82:10,13,15,21 82:23 83:8,11 83:19,21,22 84:18,24 85:6 85:12,13 86:13 86:14,17 87:16 87:17,22,24 88:18 89:14 90:4 92:10	96:2,23 99:13 101:19 131:4 133:3 138:6 139:12 141:7 142:4,8,14,17 142:17 151:9 153:15 155:6 155:15 156:18 156:23 161:23 161:24 subject 9:18 11:14 22:17 38:14,18 39:4 39:18 45:5 58:24 59:9 65:7 124:22 subjected 96:6 145:19 subjects 82:16 153:15 155:6 155:15 157:1 157:19 159:2 159:11 160:22 161:7 submitted 5:24 6:14 7:8 8:2,7 8:10,11,20 26:17,22 27:20 submitting 31:5,21,24 subscribed 167:14 substance 23:5 23:11	substantially 116:3 subtype 60:21 subtypes 61:2 success 154:10 successful 51:16 sufficient 35:18 46:18 47:1 50:1 52:13 suggest 129:24 suggesting 124:13,19 suggests 52:8 suitable 123:12 suited 98:2 sullivan 2:10 summarize 78:19 summary 97:20 97:21,24 114:9 superior 82:4 support 6:15 61:16 104:3 153:14,20 155:14 supported 70:20 114:10 155:5 156:14 sure 4:10,21 5:3,16 23:15 29:5 44:3 45:24 56:16 59:6 62:4	68:19 98:12 118:11 124:11 125:11 128:6 136:10 137:5 137:14,15 144:12 150:7 152:7 surgeons 65:20 surgery 65:20 65:21 66:7 94:23 97:5 surprise 19:8 19:20 survey 75:7 159:12 161:8 survival 45:23 65:24 68:22 sweet 67:12 sworn 4:1 167:14 symptomatic 45:21 134:9 symptoms 45:10 68:21,21 synergy 110:24 system 80:21
			t
			t 2:4 3:6 121:18 121:19 166:3,3 table 38:21,24 39:5,10 92:5,8 92:22 93:1,5 93:11,16

101:20,20,20 108:7,9,12 tables 101:20 take 5:9,10,12 5:12,15 12:6 13:2 20:12 24:7 44:2 55:2 56:15 65:4 114:1 119:14 162:3 taken 1:14,16 35:6 103:8 takes 76:16 talk 13:10 32:17 36:20 39:2 53:18 59:6 60:10,12 60:13,15 64:1 64:2,4,15 65:9 73:18 84:21 89:22 101:15 101:16 105:7 107:17 143:17 143:17 talked 13:14 15:14 58:6 84:14 146:23 talking 4:18 41:23 63:13 90:9 117:7 132:16 141:14 148:7 talks 57:12	target 70:24 73:9 83:12,22 146:15 task 117:16 teach 53:22 teaching 121:10 technical 6:19 8:1 9:21 technically 34:9 technique 47:18,18 techniques 47:16 48:12 technology 35:13 36:16 tell 11:5 70:9 tells 102:4 temperature 131:10 terminology 89:7 162:12 terms 54:15 terrible 117:22 tertiary 81:12 test 3:16,17 15:24 18:22 19:11 46:10 48:18,20 49:10 50:13,15 51:20 52:22 53:2,8 53:10 54:18 55:4,15 56:24	57:9 59:15 61:16,19,23 66:17 69:6 70:24 72:23 73:22,23 74:8 74:9 76:3,4,14 76:20 77:6,13 79:3,15,23 80:5 82:5 83:12,23 84:2 84:10 85:23 86:1 89:15 90:7,18,18 92:15,16 93:3 93:6,7 94:16 94:16 96:2,3,6 96:12 99:2 100:24 101:9 101:11 103:3,8 103:15,20 106:23 109:11 111:20,22 112:10,10,13 112:14,24 113:3,6,9,14,20 114:14 117:18 117:21 118:5 119:24 121:18 122:3 125:11 125:21 127:5 129:24 131:17 131:18 133:13 133:22 134:6 135:19 136:21	136:22 137:12 138:10 143:6 153:9,17 154:10,20,22 155:8,17 156:21,21,24 157:9 158:8,10 158:12,19,23 159:7,18,23 160:12,13,14 160:18,23 161:10,13,15 162:13,19,20 163:1,2 tested 50:22 72:10 91:22 92:2 96:11,15 96:21 99:16 100:3 105:15 114:13 115:2,5 115:9,10,13 128:20 130:20 134:17 145:23 160:22 testify 53:17 testimony 8:14 8:16 9:3 165:9 165:17 167:8 testing 71:11 71:13,24 72:16 72:18 73:10 84:6 95:23 132:12 133:6 135:5,12,19
---	--	--	--

139:7 153:16 155:7,16 159:16,22 160:4,18 161:2 161:5 tests 15:19 45:13 46:8 50:4 51:2,7,7 51:11 61:5 64:3 68:4 75:12,22 80:17 113:10 120:18 121:1,11,13,13 121:16,16 122:19,23,24 123:4 125:7 132:10,17,20 137:4 140:9 145:19 153:8 161:4 162:22 text 57:7 thank 20:14 35:19 74:6 75:17 118:24 thanksgiving 10:21,24 therapeutic 47:10 65:12 therapeutics 39:7,21 thereof 12:17 thereto 30:7 thing 18:20 50:19 58:10	69:3 85:5 106:10 116:16 121:21 158:23 things 12:15 13:10 19:22 23:19 69:13 112:19,20 117:7 118:21 125:21 131:9 149:17 think 6:8,9 9:14 10:2,22 14:13 15:1,2 16:8,18,21,21 17:15 21:15 23:2 24:16 26:13,23 30:3 31:20 32:4,19 32:21 33:12,19 33:20 34:8 35:22 38:12 40:11 46:19 56:6,20 57:1 57:18 58:7,8 58:13 59:16 62:7,22 63:1 63:20 65:5 68:13 74:18 75:15 76:10 78:15,19 84:13 88:7 89:9,20 90:16 96:8,13 96:17,17 97:2 97:14 99:24	104:1,10,11 105:5,6,11,20 106:1 107:1 108:7 111:4,5 111:15,16 112:15,17 115:15 116:4 117:24 118:20 125:12 126:1 126:11 127:23 129:23 131:20 132:1 135:24 136:7,9 137:22 139:10,22,23 140:20,21 141:20 142:23 145:3,4 146:7 149:15,17 150:4 158:9 159:9 thinking 18:21 106:12 thinks 14:15 142:6 third 48:3 49:9 103:15 158:23 158:23 160:12 thirds 72:13 94:2 101:1 102:13 115:24 117:14 153:12 thornburg 1:17 thought 14:20 15:4	thousand 161:9 three 25:13 69:13 103:21 113:10,11 127:21 130:2 132:10,17,20 132:20,22,23 136:1 137:10 137:11 138:15 138:15,18,18 138:19 139:2,6 139:12,16,20 140:8,10,19,23 140:24 141:4,5 141:8,10 142:5 142:12 157:24 158:14 161:9 threshold 121:7 123:12 136:14 137:20 141:22 thresholds 126:15 136:21 tier 50:15 time 4:8,18 14:3 17:8,11 17:24 18:6,11 18:18,21 19:6 19:7,9,12,21 21:18,18 27:12 28:8,16,18,22 29:6 34:15 36:18 37:20 38:2,3,4,8 39:9
--	---	--	---

41:11 43:11 47:12 48:16,22 50:7,11 51:14 52:2,6,8 54:5 54:13,21 56:3 56:5,15 58:1 65:15 68:22 79:14,14,20 88:12,15 106:4 106:5,6 111:23 125:24 128:3 130:14 165:18 timeframe 31:23 42:9 43:14 165:8 timeline 12:1,3 12:6,10,12 times 20:15 24:24 58:14 60:18 81:17 82:24 titled 91:9 143:5 144:5 today 5:18 7:12 23:4 24:1 51:14 79:23 80:8 together 20:4 103:4,8,22,24 104:8 110:16 113:20 115:6 115:13 150:8 151:11,16	toilet 157:4 told 13:4,6,8,15 13:24 14:2 16:23 20:21 136:5 tolerated 49:6 tool 83:12,23 top 70:16 114:3 123:6,23 topics 38:17 tossing 78:11 total 28:22 159:11 towards 106:12 tract 50:22 trade 151:22 trademark 1:1 trained 124:9 125:2,10 transcript 9:9 9:10,12 10:6 32:24 33:5,14 33:22 134:13 164:6 165:6,19 167:5,8 transcripts 9:6 9:12 33:10 translate 87:15 translated 98:21 transport 147:6,22 traps 111:3	treated 67:3 trial 1:2 21:20 59:22 81:1,6,7 82:9,14 85:6 86:7,8 89:9 112:9 114:8,8 trials 19:4 83:1 84:15,22 88:11 88:17 tried 47:16 true 108:14 164:6 167:8 truthful 5:18 try 100:16,16 104:20 trying 18:11,12 59:12,17,17 80:7 103:12 133:12 134:5 139:23 tube 127:7 tumor 67:1,9 turn 27:23 29:13 44:6 46:12 71:3 91:13 120:9 126:21 142:23 turning 27:17 turns 89:1 twice 113:7 135:22 two 5:20 16:8 19:22 20:3,3 22:6,14 24:5	24:10,12 25:4 25:5,11,12,15 25:16 32:16 52:1,1 72:13 94:2 101:1,13 102:13 110:1 110:11,13,21 112:19,20,20 113:2 115:20 115:24 117:6 117:14 121:20 126:7 135:3,22 136:6 139:2,14 148:16 149:17 149:18 150:14 150:22 151:19 152:2,11,11,15 153:12 157:23 158:13 type 157:3 types 41:16 113:11 typically 67:5 76:13 100:15 122:19 123:3 125:17 134:20
			u
			u.s. 1:8 7:9 31:10 uh 32:12 36:3 37:6 55:17 69:17 70:19 73:4 92:7

94:24 97:18 112:12 141:16 144:3,6 unacceptable 44:23 unchanged 102:21 under 15:17 48:15 57:3 60:11 71:3 77:7 80:13 101:16 103:5 120:11 131:23 143:20 148:5 156:18,23 undergo 48:6 49:19 81:21 understand 4:20 5:2,5 7:13 7:15,19,20 8:6 20:19 23:15,16 40:15,15 53:20 54:5,11,19 57:12 81:4 85:22 90:12 114:7 117:13 126:20 understanding 5:6,22 54:2 97:15 141:6 understood 5:6 50:11 89:12 90:17 137:15	underwent 159:3,4 undetectability 50:16 unh 37:24,24 united 1:1 135:4,11 140:16 unnecessary 44:24 unquote 90:13 unsealed 145:9 untreated 45:6 45:9,17 uptake 46:9 50:5 60:12 69:12 103:16 117:5 urgently 60:24 urquhart 2:10 use 43:22 50:23 61:5 70:15 80:19 85:7 88:8 90:10 94:15 97:14 98:10 112:7 138:10 157:21 used 9:20 35:2 50:14 51:4 59:14 75:15 76:13 84:20 88:12,15,17,19 88:22 89:10 96:19 98:15	107:16 111:13 111:16,18 112:3,4 122:20 127:6,10 133:13,19 134:1,6 135:4 136:20 137:20 138:16 165:19 useful 128:3 using 40:14 96:2 127:16 141:17 147:5 147:21 148:8,9 149:6 157:2,5 usually 45:10 49:10 utilization 46:10 51:22 103:16 v v 165:4 166:1 167:1 vadim 1:14 3:8 3:9 4:1 165:5 166:2,24 167:2 167:4,12 vague 68:12 112:16 validated 114:14 validation 59:22 151:6,13	valuable 52:17 78:24 value 46:18 47:1 76:17 132:11 values 101:21 101:21,24 variability 87:10 variety 18:1 38:17 49:7 vary 67:15 verify 165:9 veritext 165:14 165:23 veritext.com 165:15 versa 49:17 version 146:14 146:23 147:2,8 147:15 148:11 148:16 152:1,4 152:15 versions 145:22 versus 68:15 69:2 74:13 75:24 77:9,13 102:11 110:14 116:14,19 124:20 138:18 138:19 161:23 vessel 144:11 vice 49:17
---	--	---	--

view 18:24	88:10 106:1	9:5	works 86:3
vilkin 119:20	134:22 137:4	widely 51:4	89:15 111:9
120:5,6,9,12,23	137:23 139:1	witness 11:9	worse 103:6,11
121:3,10,13	142:23 150:7	155:24 162:6,8	105:2 108:20
123:24 124:7	wanted 18:19	164:8 165:8,10	111:2 115:12
124:13 125:12	19:2 68:5	165:12,18	worst 109:4
126:6,8,11	134:3	witnesses 10:19	write 27:3 28:2
127:6,10,14	wants 74:24	word 65:10	44:21 135:2
136:19 137:9	way 14:23	75:15 88:8,19	writing 28:19
137:18 138:9	18:19 28:21	88:22 89:8,9	57:11
138:13,23	35:8,14 36:1	89:11 90:10	written 61:13
139:5 161:14	47:19,19 61:13	107:16 134:3	64:11 106:3
161:24	72:13 81:18,19	135:21 136:2	125:24
vilkin's 123:16	89:24 100:2,15	141:20 142:16	wrong 75:15
125:24 127:14	100:20 105:8,9	words 84:20	83:14 134:12
vimentin	109:22,23	105:8	wrote 105:9
145:24 148:17	112:2,3 114:13	work 13:6,12	x
148:20 149:2,7	133:11 136:5	13:15,24 14:4	x 3:1,6
150:10,12,23	142:18 153:12	14:8,9,13,21	y
visual 145:9	ways 47:14	15:1,4,6,13	yeah 5:3 6:1,8,8
volunteered	we've 44:1	20:22 27:5	6:9,18 7:14
17:10,16,21	weed 48:7	28:13 30:17	8:19 9:4 11:17
20:4	week 23:1 24:6	36:20 37:15	22:13,23 23:1
vs 1:7	25:6	38:9,15,23	25:7,13 26:19
w	weeks 24:9,11	40:9,11,13,24	28:1 31:3
wacker 1:17	24:12,12 35:11	41:1,2 43:1,7	36:23 40:22
wait 4:14 29:3	went 19:8,23	70:10 77:18	43:10 45:3
83:14	30:1,1 159:4	81:13 114:16	62:12 70:13,22
want 39:1,16	whereof 164:8	133:22 143:16	72:22 73:7,7
41:4 44:13	whitney 8:4,11	150:24 156:14	73:14,18 79:8
49:7 64:22	9:12 30:9 33:2	worked 22:3	83:9 91:5,17
69:5 74:2	33:6,10	working 21:17	94:4,18 96:17
75:14 85:7	whitney's 8:6	34:15 36:18	104:19 111:15
	8:14,15,17 9:2	37:18 54:20	

127:2 128:6
135:8 143:7,24
145:13 152:7
152:11 160:24
161:6
year 18:7 36:9
39:9 43:17
45:20,23 67:16
67:17 132:17
132:23 135:20
135:22 137:4
137:23 138:18
138:19 139:1,2
139:2,3 141:5
years 38:13
54:18 66:8
67:19 135:22
136:1,6
yep 91:16
yesterday
25:20,21
york 2:11
young 111:4
z
ziploc 129:13
ziplock 129:1
zoom 12:23
13:23 16:3,5,9
16:12,13,16,19
17:1,4 22:7,14
24:5,7,22

Federal Rules of Civil Procedure

Rule 30

(e) Review By the Witness; Changes.

(1) Review; Statement of Changes. On request by the deponent or a party before the deposition is completed, the deponent must be allowed 30 days after being notified by the officer that the transcript or recording is available in which:

(A) to review the transcript or recording; and

(B) if there are changes in form or substance, to sign a statement listing the changes and the reasons for making them.

(2) Changes Indicated in the Officer's Certificate. The officer must note in the certificate prescribed by Rule 30(f)(1) whether a review was requested and, if so, must attach any changes the deponent makes during the 30-day period.

DISCLAIMER: THE FOREGOING FEDERAL PROCEDURE RULES ARE PROVIDED FOR INFORMATIONAL PURPOSES ONLY.

THE ABOVE RULES ARE CURRENT AS OF APRIL 1, 2019. PLEASE REFER TO THE APPLICABLE FEDERAL RULES OF CIVIL PROCEDURE FOR UP-TO-DATE INFORMATION.

VERITEXT LEGAL SOLUTIONS

COMPANY CERTIFICATE AND DISCLOSURE STATEMENT

Veritext Legal Solutions represents that the foregoing transcript is a true, correct and complete transcript of the colloquies, questions and answers as submitted by the court reporter. Veritext Legal Solutions further represents that the attached exhibits, if any, are true, correct and complete documents as submitted by the court reporter and/or attorneys in relation to this deposition and that the documents were processed in accordance with our litigation support and production standards.

Veritext Legal Solutions is committed to maintaining the confidentiality of client and witness information, in accordance with the regulations promulgated under the Health Insurance Portability and Accountability Act (HIPAA), as amended with respect to protected health information and the Gramm-Leach-Bliley Act, as amended, with respect to Personally Identifiable Information (PII). Physical transcripts and exhibits are managed under strict facility and personnel access controls. Electronic files of documents are stored in encrypted form and are transmitted in an encrypted

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