

1 UNITED STATES PATENT AND TRADEMARK OFFICE
2 BEFORE THE PATENT TRIAL AND APPEAL BOARD
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4

5 GENE COMPANY PTY LTD.,

6 Petitioner,

7 vs.

No. IRP2024-00313;
Patent No. RE47,045

8 THE TRUSTEES OF COLUMBIA
9 UNIVERSITY IN THE CITY
10 OF NEW YORK,
11
12

13 Patent Owner.
14 _____/

15 DEPOSITION OF ANDREW CALMAN, M.D., PH.D.
16
17

18 August 27, 2024
19
20
21

22 Taken before EARLY K. LANGLEY, RMR, B.A. (PBK)
23

24 CSR No. 3537
25

Job No. YOM 6839149

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I N D E X

WITNESS

ANDREW CALMAN, M.D., PH.D.

Examination By Mr. Feldstein 7

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Exhibit 2071	Document from web page	147
titled "Andrew F.		
Calman, M.D., Ph.D.		
Contact this Expert		
Witness"		

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DEPOSITION OF ANDREW CALMAN, M.D., PH.D.

BE IT REMEMBERED, that pursuant to Notice, and on August 27, 2024, commencing at the hour of 9:08 a.m., in the offices of Wilson, Sonsini, Goodrich & Rosati, One Market Plaza, San Francisco, California, before me, EARLY LANGLEY, a Certified Shorthand Reporter, State of California, personally appeared ANDREW CALMAN, M.D., PH.D., produced as a witness in said action, and being by me first duly sworn, was thereupon examined as a witness in said cause.

---000---

APPEARANCES:

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1	--oOo--	
2	P R O C E E D I N G S	
3	--oOo--	09:08
4	MR. FELDSTEIN: We'll go on the record.	09:08
5	Good morning, Doctor. Mark Feldstein from	09:08
6	Finnegan Henderson on behalf of the Patent Owner.	09:08
7	How are you?	09:08
8	THE WITNESS: Good morning. Fine.	09:08
9	MR. FELDSTEIN: You have before you all of	09:08
10	your exhibits from both of the two IPRs,	09:08
11	IPR2024-00312 and 00313; correct?	09:08
12	THE WITNESS: I believe so.	09:08
13	ANDREW CALMAN, M.D., PH.D.	09:08
14	sworn as a witness,	09:08
15	testified as follows:	09:08
16	EXAMINATION BY MR. FELDSTEIN:	09:08
17	Q. For simplicity, I'm going to focus on and	09:08
18	refer to exhibits from the IPR-00313 and use the	09:08
19	exhibits from those. They overlap, but if there's	09:08
20	any confusion, I'm going to focus on the 313 for	09:08
21	today.	09:09
22	A. Well, unfortunately, my binder primarily	09:09
23	is keyed to the '432 declaration.	09:09
24	Q. Okay. Well, fortunately, we have copies	09:09
25	of everything.	09:09

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1	A. So we may need to use the exhibit numbers	09:09
2	from -- well, I guess the exhibit numbers are the	09:09
3	same.	09:09
4	Q. We'll just give you the exhibits.	09:09
5	A. Yeah, that will work.	09:09
6	MR. MILLS: The exhibit numbers should all	09:09
7	be the same.	09:09
8	BY MR. FELDSTEIN:	09:09
9	Q. Do you have your declaration from the 313	09:09
10	IPR, Exhibit 1004?	09:09
11	A. I do.	09:09
12	Q. Okay. Good.	09:09
13	Can you turn towards the back of your	09:09
14	declaration, Exhibit 1004, to pages 119 to the	09:09
15	end. This is a list of the materials you cited in	09:09
16	this report; correct?	09:09
17	A. Yeah, that what it appears to be, yes.	09:09
18	Q. Can you identify which of the exhibits	09:09
19	that are listed that you were aware of before you	09:09
20	began work on this case?	09:10
21	A. Hmm. Okay. Well, my CV, obviously.	09:10
22	Q. So, then, if you don't mind, by number?	09:10
23	A. 1005.	09:10
24	Q. Okay.	09:10
25	A. I was aware of some of the information in	09:10

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1	1010. I don't know if I -- I don't think I read	09:10
2	the original paper.	09:10
3	Q. Okay.	09:10
4	A. I probably referred to 1017 before. It's	09:10
5	a large tome. But I certainly haven't read the	09:10
6	whole thing.	09:10
7	1022, I was certainly aware of.	09:10
8	I may have read 1029. He's written a lot	09:11
9	of papers on the subject.	09:11
10	1040.	09:11
11	1055.	09:12
12	I'm sure I've seen 1059 or the equivalent	09:12
13	from the American Academy of Ophthalmology.	09:12
14	Q. Of the remainder of the exhibits that you	09:12
15	didn't identify as having previously considered,	09:12
16	are there any that you can recall that you	09:12
17	provided to your counsel in this case as opposed	09:12
18	to vice versa?	09:12
19	A. Yes.	09:12
20	Q. Could you identify those?	09:12
21	A. So this is going to be an incomplete list	09:12
22	because I don't have a perfect memory of which	09:12
23	ones I found.	09:12
24	I am not sure. Possibly, 1020 and 1021.	09:12
25	1022, for sure.	09:13

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1	1025.	09:13
2	I'm not sure about 1027.	09:13
3	1028, I'm not sure about that.	09:13
4	1029, I think I also was the who found --	09:13
5	Q. I'm sorry. You said for 1028, you're not	09:13
6	sure?	09:13
7	A. I'm not sure, but that may have been one	09:13
8	of the ones that I identified.	09:13
9	And, again, my memory on this is not	09:13
10	perfect, so there may be others that I have not	09:13
11	mentioned. I'm still going here.	09:14
12	Possibly, 1039.	09:14
13	1040, again, not a hundred percent sure on	09:14
14	that.	09:14
15	I think I found 1041.	09:14
16	I think I found 1042.	09:14
17	I think I found 1043.	09:14
18	1055.	09:14
19	And 1059, I believe I found that one, too.	09:15
20	Q. Thanks.	09:15
21	Do you have expertise in the biological	09:15
22	processes of lipofuscin formation?	09:15
23	A. Well, I have a background in molecular	09:15
24	biology and biochemistry, and I diagnose and treat	09:15
25	retinal disease. So I have -- I have a background	09:15

1 in the -- an understanding of retinal physiology, 09:15
2 but I do not independently conduct research in 09:15
3 that area. 09:15
4 Q. So you have a background, but you don't 09:15
5 consider yourself an expert in the biosynthetic 09:15
6 formation of lipofuscin formations; is that 09:15
7 correct? 09:15
8 MR. MILLS: Objection to form. 09:15
9 THE WITNESS: I would say there are levels 09:15
10 of expertise. I think I have a higher level of 09:15
11 expertise than the average ophthalmologist, but I 09:15
12 do not have the same level of expertise as someone 09:15
13 who is working in a lab on that subject. 09:15
14 BY MR. FELDSTEIN: 09:15
15 Q. And do you have expertise in the -- in 09:15
16 Stargardt's disease? 09:16
17 A. I'm an ophthalmologist who diagnoses and 09:16
18 treats patients with macular disease. That said, 09:16
19 this is a rare disease, and I don't have the same 09:16
20 level of expertise as someone whose practice, for 09:16
21 example, is primarily confined to treatment of 09:16
22 retinal dystrophies. 09:16
23 Q. What level of expertise do you have in 09:16
24 Stargardt's disease? 09:16
25 A. Well, I have the level to diagnose it and 09:16

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1	make the appropriate referral, and I have an	09:16
2	understanding of the disease process.	09:16
3	Q. So you, yourself, don't treat Stargardt's	09:16
4	disease; is that correct?	09:16
5	A. Well, I mean, we don't really have an	09:16
6	effective treatment other than patients who have	09:16
7	choroidal neovascularization. So I may make	09:16
8	recommendations on lifestyle modifications, but	09:17
9	typically, I refer those patients to the	09:17
10	university, where there is a person who treats and	09:17
11	diagnoses exclusively inherited retinal disease.	09:17
12	Q. And the specific person?	09:17
13	A. Yes.	09:17
14	Q. Who is that?	09:17
15	A. Dr. Jacque Duncan, J-a-c-q-u-e	09:17
16	D-u-n-c-a-n, at the University of California San	09:17
17	Francisco.	09:17
18	Q. And how long have you been in practice,	09:17
19	Doctor?	09:17
20	A. I have been in practice since 1993. So	09:17
21	about 31 years.	09:17
22	Q. And, roughly, how many Stargardt's	09:17
23	patients have you seen in 31 years?	09:17
24	A. Less than ten.	09:17
25	Q. Is it kind of spread out over that	09:17

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1	31 years?	09:17
2	A. Yes.	09:17
3	Q. What lifestyle changes do you recommend	09:17
4	for Stargardt patients?	09:17
5	A. If they're smoking, I recommend that they	09:17
6	stop. I recommend that they wear -- that they	09:18
7	have UV protection in their glasses. I recommend	09:18
8	that they wear sunglasses and/or a hat when	09:18
9	they're outdoors and minimize exposure to excess	09:18
10	sunlight. And I recommend that they not consume	09:18
11	excessive vitamin A.	09:18
12	And beyond that, I typically refer them to	09:18
13	Dr. Duncan so that they can have the benefit of	09:18
14	her advice as well.	09:18
15	Q. And the guidance you just gave on smoking,	09:18
16	UV protection, sunglasses, and not consuming	09:18
17	excess vitamin A, is that unique to be treating	09:18
18	Stargardt's or to Stargardt's patients, or is that	09:18
19	the recommendation for other conditions also?	09:18
20	A. So the smoking -- for other macular	09:18
21	degenerations, including other macular dystrophies	09:18
22	and age-related macular degeneration, we recommend	09:18
23	no smoking, and we recommend UV protection in	09:19
24	their glasses, and we recommend sun protection if	09:19
25	they are going to be outdoors.	09:19

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1	But the vitamin A dietary -- avoiding	09:19
2	excess dietary vitamin A is the recommendation	09:19
3	specifically for Stargardt's.	09:19
4	Q. And why is that a recommendation	09:19
5	specifically for Stargardt's?	09:19
6	A. Because Stargardt's has a genetic defect	09:19
7	that results in accumulation of lipofuscin	09:19
8	precursors.	09:19
9	Q. I'm sorry. Can you connect the dots for	09:19
10	me why the instructions are not to consume excess	09:19
11	vitamin A for patients with this genetic disorder?	09:19
12	A. Because of the potential for exacerbating	09:19
13	the buildup of all-trans-retinal, r-e-t-i-n-a-l,	09:19
14	which is the precursor to lipofuscin in the	09:20
15	retina.	09:20
16	Q. And how would excess vitamin A build up	09:20
17	ATR?	09:20
18	A. Well, potentially, the -- you know,	09:20
19	basically, the more substrate you're inputting	09:20
20	into the visual cycle, potentially that's	09:20
21	exacerbating the buildup of ATR, which is the	09:20
22	lipofuscin precursor.	09:20
23	Q. AND just for the reader later, I	09:20
24	introduced the acronym ATR. That was to	09:20
25	correspond to what you had more fully identified	09:20

1	as all-trans-retinal?	09:20
2	A. Yes.	09:20
3	Q. And how does vitamin A -- how does vitamin	09:20
4	A exacerbate the buildup of ATR?	09:21
5	A. I think that's the same question you just	09:21
6	asked.	09:21
7	Q. Maybe it was.	09:21
8	Can you explain what you meant when you	09:21
9	said that more substrate inputted into the visual	09:21
10	cycle potentially exacerbates the buildup of ATR?	09:21
11	A. Well, in chemical reactions generally, if	09:21
12	you increase the input of the initial reactant,	09:21
13	you are going to -- you are going to shift the	09:21
14	equilibrium toward the end products; you are going	09:21
15	to increase -- potentially increase the buildup of	09:22
16	the end product, which in this case is ATR and its	09:22
17	harmful lipofuscin products.	09:22
18	Now, we're oversimplifying here a little	09:22
19	because dietary, obviously -- and I discuss this	09:22
20	in my report.	09:22
21	Dietary vitamin A is absorbed in the gut,	09:22
22	usually in the form, most commonly, of beta	09:22
23	carotene, and there are enzymatic reactions in the	09:22
24	gut. There are enzymatic reactions in the retina	09:22
25	and RPE involved in the visual cycle.	09:22

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1	I'm sort of streamlining. I'm	09:22
2	oversimplifying a little bit.	09:22
3	Q. And does -- the recommendation to	09:22
4	Stargardt's patients to avoid excess vitamin A,	09:22
5	does it depend on whether they're vitamin A	09:22
6	deficient or whether they have a healthy amount of	09:23
7	vitamin A in the system already?	09:23
8	A. There is certainly a spectrum, and I think	09:23
9	Dr. Sommer or one of the other authors that we	09:23
10	cite identify five different levels of vitamin A	09:23
11	status, from extremely deficit to overabundant.	09:23
12	And they use, I think, different terms for that.	09:23
13	Certainly, vitamin A deficiency has its	09:23
14	own problems, including xerophthalmia, so an	09:23
15	extreme absence of vitamin A is also undesirable.	09:23
16	But, you know, clearly, the idea here is to avoid	09:23
17	the extremes.	09:23
18	Q. So is it the case that if you have a	09:23
19	healthy level of vitamin A -- if you are a	09:24
20	Stargardt's patient and you have a normal level of	09:24
21	vitamin A, that taking more vitamin A runs the	09:24
22	risk of creating more ATR?	09:24
23	A. So I don't know that that experiment has	09:24
24	ever been done to fully verify that, but that	09:24
25	is the -- that is the thinking in the current --	09:24

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1 at the current time. 09:24

2 Q. And what's the origin of this concern that 09:24

3 vitamin A -- is it fair to say that vitamin A is 09:24

4 contraindicated for Stargardt's patients? 09:24

5 MR. MILLS: Objection to form. 09:24

6 THE WITNESS: So I think, again, we're 09:24

7 talking -- it sounds like we are talking about 09:24

8 present day. 09:24

9 I think you said, "vitamin A is 09:24

10 contraindicated." 09:24

11 As I talked about a minute ago, you don't 09:24

12 want to have a condition of vitamin A deficiency 09:24

13 because there are potentially other problems, such 09:24

14 as xerophthalmia. And we didn't mention it, but 09:25

15 also night blindness is a potential side effect of 09:25

16 vitamin A deficiency. 09:25

17 But the concern is that higher levels of 09:25

18 vitamin A may cause more rapid accumulation of 09:25

19 lipofuscin products. 09:25

20 And so the precise level of vitamin A, to 09:25

21 the best of my knowledge, has not been worked out 09:25

22 experimentally, but most clinicians, as far as I 09:25

23 know today, do not recommend vitamin A 09:25

24 supplementation for Stargardt's. 09:25

25 Q. And is it, in fact, they recommend against 09:25

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1	vitamin A supplementation for Stargardt's?	09:25
2	A. So I haven't seen an official, you know,	09:25
3	organizational recommendation on that. But my	09:25
4	understanding of how people practice currently is	09:25
5	that that is the case.	09:25
6	Q. And was that the same or different in the	09:25
7	2007-2008 period?	09:25
8	A. So to the best of my recollection from	09:26
9	practicing in that time period, there were no	09:26
10	formal recommendations at that time. But there	09:26
11	was evidence in the literature, at least in the	09:26
12	animal literature, that -- and I can actually, if	09:26
13	I may, go to...	09:26
14	Just make sure I remember what the	09:26
15	question is here.	09:26
16	Q. I can rephrase it when you're ready. Let	09:26
17	me know when you've found whatever you are looking	09:26
18	for.	09:26
19	A. So just to summarize -- and if you want me	09:26
20	to go into more detail, we can do that, but I will	09:26
21	want to read the whole paper again.	09:26
22	Q. And what paper are you looking at?	09:26
23	A. Mata 2000, which is Exhibit --	09:26
24	Q. It's the bottom right corner. 1010?	09:26
25	A. -- 1010.	09:26

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1	And what they showed was that abcr-/-mice,	09:26
2	which were basically an animal model, mouse model,	09:27
3	showing -- of Stargardt's with a knockout of the	09:27
4	abcr gene.	09:27
5	When they were reared in darkness, they	09:27
6	were unable to detect A2E, and when they were	09:27
7	reared in light, they did form A2E.	09:27
8	And interestingly, if they were initially	09:27
9	reared in darkness and then put into light --	09:27
10	excuse me -- if they were initially reared in	09:27
11	light condition and then put into darkness, they	09:27
12	still had the same amount, roughly, of A2E,	09:27
13	suggesting that in the absence of the life cycle,	09:27
14	A2E did not form and that once it was formed, it	09:27
15	was not removed from the eye.	09:27
16	Q. So to your understanding, is Mata,	09:27
17	Exhibit 1010, the origin for the current practice	09:28
18	of recommending against vitamin A supplementation	09:28
19	for Stargardt's patients?	09:28
20	MR. MILLS: Objection to form.	09:28
21	THE WITNESS: I think that line of	09:28
22	research is certainly one of the bases for that.	09:28
23	And I believe there were some other	09:28
24	experiments as well. If you look at Exhibit 1011,	09:28
25	Fishkin, 2005, there were some additional	09:28

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1	experiments there, including --	09:28
2	And, again, if you want me to go into	09:28
3	detail, I will do so, but I'm going to need to	09:28
4	read the whole paper.	09:28
5	But they also looked at human donor eyes	09:28
6	as well in Stargardt's patients -- not donor eyes,	09:28
7	but I believe they looked at some postmortem eyes	09:28
8	from Stargardt's patients.	09:28
9	You know what, let me read the paper.	09:29
10	BY MR. FELDSTEIN:	09:29
11	Q. Can I ask you the question that I am	09:29
12	looking for --	09:29
13	A. Yeah.	09:29
14	Q. -- where we went off track a little bit?	09:29
15	A. Did you get what I said, "postmortem eyes	09:29
16	of Stargardt's patients."	09:29
17	Q. The question I asked before you had turned	09:29
18	to Mata was: Was it also the practice in the	09:29
19	2007-2008 period to recommend against vitamin A	09:29
20	supplementation for Stargardt's patients?	09:29
21	A. Yeah, I don't think there -- I think I	09:29
22	sort of answered that already. I don't believe	09:29
23	there were any formal recommendations, and I think	09:29
24	that those who were aware of some of this	09:29
25	experimental literature might have thought that	09:29

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1	restriction of vitamin A could be helpful in these	09:29
2	patients.	09:29
3	But, you know, I don't have a precise	09:29
4	recollection of exactly what the thinking was in	09:29
5	2007 on that specific point, nor have I found a	09:29
6	specific reference in that 2007 time frame that	09:29
7	directly addresses that question.	09:30
8	Q. And when you saw Stargardt's patients in	09:30
9	the 2007-2008 period, was your practice to	09:30
10	recommend against vitamin A supplementation?	09:30
11	A. My practice at that time would have been	09:30
12	to recommend no smoking, UV protection, sunglasses	09:30
13	in bright light.	09:30
14	And I would have not recommended any	09:30
15	specific supplementation, but I probably would	09:30
16	have deferred any dietary recommendations to	09:30
17	Dr. Duncan, after referring the patient to that	09:30
18	subspecialist for specific recommendations.	09:30
19	Q. And today, do you counsel Stargardt's	09:30
20	patients against taking vitamin A supplementation?	09:30
21	A. Yes.	09:30
22	Q. And did something change between 2007-2008	09:30
23	and today that provides the basis for your current	09:30
24	recommendation to Stargardt's patients to not take	09:31
25	vitamin A supplementation?	09:31

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1 A. Yeah, I can't specifically point to a 09:31
2 specific paper or recommendation, but -- or a 09:31
3 specific date when it became more prevalent for 09:31
4 people to practice in this way, but I think it has 09:31
5 become accepted in the field that these patients 09:31
6 should not receive vitamin A supplementation. 09:31
7 Q. Is ATR buildup also an issue in dry 09:31
8 age-related macular degeneration? 09:31
9 A. I'm not sure. I guess you'd have to 09:31
10 define "ATR buildup." 09:31
11 Q. You had talked earlier in terms of 09:31
12 Stargardt's patients that you were avoiding 09:31
13 vitamin A supplementation to avoid creating more 09:31
14 intermediate that can form into A2E and, 09:32
15 specifically, ATR. Was that essentially what you 09:32
16 testified to earlier? 09:32
17 A. That is a rough approximation, yeah. 09:32
18 Q. And so my question now is, don't you have 09:32
19 the same intermediates, including ATR, building up 09:32
20 in dry age-related macular degeneration patients? 09:32
21 A. That's a little bit of a different 09:32
22 question, but... 09:32
23 The difference is that in Stargardt's, you 09:32
24 have a defect in the ABCA4 gene, or ABCR, and, 09:32
25 therefore, the ATR is unable to be promptly 09:32

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1	transported to the RPE for further metabolic --	09:32
2	it's more complicated than that, because it gets	09:32
3	conjugated with phosphatidylethanolamine, or PE.	09:32
4	In any case, that defect is -- although	09:33
5	some patients with AMD, which is age-related	09:33
6	macular degeneration, may have ABCR gene defects,	09:33
7	most do not. And if they do, they're usually	09:33
8	heterozygous.	09:33
9	So in general, with some exceptions, most	09:33
10	patients with AMD, the ATR is able to go through	09:33
11	the normal life cycle, which involves both the rod	09:33
12	outer segments and the RPE, which is retinal	09:33
13	pigment epithelium.	09:33
14	So it's a different problem, and it's a	09:33
15	somewhat different situation than Stargardt's.	09:33
16	Q. So is lipofuscin accumulation not an issue	09:33
17	for AMD?	09:33
18	A. Oh, of course it's an issue. But it tends	09:34
19	to occur at a later age, and the problem is not so	09:34
20	much that there's rapid formation of lipofuscin in	09:34
21	AMD. The problem is that there's accumulation	09:34
22	over a longer period of time, which is -- you	09:34
23	know, this is a disease of the elderly, for the	09:34
24	most part.	09:34
25	And so there are some common	09:34

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1	characteristics, including lipofuscin formation,	09:34
2	but it tends to manifest at a much earlier age	09:34
3	with Stargardt's because of this unique mechanism	09:34
4	due to the genetic defect.	09:34
5	Q. Is Stargardt's disease harder to treat	09:34
6	than ADM because of the genetic deficiency in	09:34
7	Stargardt's patients?	09:34
8	A. I think you mean AMD, not ADM.	09:34
9	Q. I do. Thank you.	09:34
10	A. Now, you say "harder to treat."	09:34
11	So we don't really don't have a treatment	09:35
12	for Stargardt's. We have some of those lifestyle	09:35
13	modifications that I mentioned, which may slow it	09:35
14	down somewhat, but I'm not sure we have even good	09:35
15	proof of that.	09:35
16	For AMD, we have good treatment, effective	09:35
17	treatment for what we call wet, or neovascular,	09:35
18	AMD by injecting medications called anti-VEGF.	09:35
19	That is anti-vascular endothelial growth factor.	09:35
20	For advanced dry AMD, which is	09:35
21	non-neovascular, with geographic atrophy that is	09:35
22	threatening the fovea, we now have two injectable	09:36
23	drugs that can slightly -- about 20 percent --	09:36
24	slow the progression of the disease but cannot	09:36
25	reverse it.	09:36

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1 And then we have the AREDS, which is now 09:36
2 the AREDS 2 formulation, A-R-E-D-S, which can slow 09:36
3 the transition from moderate to severe 09:36
4 non-neovascular AMD to vascular -- neovascular 09:36
5 AMD. 09:36
6 But none of those treatments can cure the 09:36
7 disease. They can, in some cases, ameliorate it 09:36
8 or slow it down. 09:36
9 Q. What are the two drugs that you have that 09:36
10 slow dry AMD by about 20 percent? 09:36
11 A. One of them is called Izervay, and the 09:36
12 other one -- Syfovre. 09:37
13 Q. Is 20 percent slowing of dry AMD pretty 09:37
14 significant, or is that kind of negligible? 09:37
15 A. So to be specific, it's approximately a 09:37
16 20 percent reduction in the rate of growth of 09:37
17 geographic atrophy in patients with dry AMD with 09:37
18 geographic atrophy threatening the fovea. 09:37
19 And opinion is divided as to how 09:37
20 significant that is clinically. 09:37
21 What I tell my patients is that this is a 09:37
22 disease that is likely -- by the time you're a 09:37
23 candidate for this treatment, you're likely to 09:37
24 have significant visual acuity reduction within 09:37
25 five years; this will give you maybe an extra 09:37

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1	year, and that's -- and that's with ongoing	09:37
2	treatments every -- injections every one to two	09:37
3	months.	09:37
4	And there are also some side effects that	09:37
5	have been reported with the drugs, so some people	09:38
6	don't use them at all.	09:38
7	Q. You use both of those drugs?	09:38
8	A. I have used them. I have -- I have	09:38
9	stopped using them.	09:38
10	Q. And what do you use in their place?	09:38
11	Anything?	09:38
12	A. Well, we don't really have anything.	09:38
13	Q. And why did you stop using it?	09:38
14	A. Because a percentage of patients will	09:38
15	develop a catastrophic vascular event resulting in	09:38
16	sudden and severe vision loss.	09:38
17	Q. The two injectables for dry AMD, about	09:38
18	when did they come onto the market and become	09:38
19	available?	09:38
20	A. About a year and a half ago.	09:38
21	Q. So other than AREDS 2, there is no	09:38
22	treatment for dry AMD today?	09:38
23	A. So, again, we have the lifestyle	09:38
24	modifications that we've talked about, and we have	09:38
25	AREDS, which is a preventive, to prevent	09:39

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1 transition primarily to -- from dry to wet, and we 09:39
2 have the two drugs that I mentioned. And that's, 09:39
3 to the best of my knowledge, the only thing that's 09:39
4 been approved for dry AMD at this time. 09:39
5 Q. Is AREDS an approved treatment, or is it 09:39
6 just a more nutraceutical category? 09:39
7 A. So first of all, there's AREDS, and 09:39
8 there's AREDS 2, and we now use AREDS 2. 09:39
9 And my understanding is that these did not 09:39
10 go through the FDA NDA process but, rather, that 09:39
11 they are -- I'm not an expert on nutraceuticals or 09:39
12 nutraceutical law or FDA law, but my understanding 09:39
13 is that they did not go through the FDA approval 09:39
14 process for a prescription drug. 09:39
15 They are available without prescriptions, 09:40
16 but they are supported by large, well-executed, 09:40
17 multicenter clinical trials. 09:40
18 Q. And biologically, what does the AREDS 2 09:40
19 treatment do to treat dry AMD? 09:40
20 A. So AREDS 2 consists of -- and this is from 09:40
21 memory, so don't -- so I may not be quite right. 09:40
22 But it's vitamin C, vitamin E, zinc, 09:40
23 copper, zeaxanthin, and lutein. So the zeaxanthin 09:40
24 and the lutein are macular pigments. Vitamin C is 09:40
25 an antioxidant, as is vitamin E. And zinc and 09:40

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1	copper, I'm not entirely sure if the actual	09:40
2	mechanism is known.	09:40
3	But those are the components, to the best	09:40
4	of my recollection.	09:41
5	Q. And biologically, how do they treat or	09:41
6	prevent progression of dry AMD?	09:41
7	A. Well, so some of this is not necessarily	09:41
8	backed up by experimental evidence because the	09:41
9	ingredients haven't been tested individually in	09:41
10	large trials the way the combinations have.	09:41
11	But antioxidants are thought to be	09:41
12	beneficial in -- in slowing the AMD process. And	09:41
13	I don't know if the details of that have been	09:41
14	worked out.	09:41
15	And lutein and zeaxanthin are macular	09:41
16	pigments, which are thought to be protective	09:41
17	against the harmful effects of excess light. And	09:41
18	I don't know that the details of that have been	09:41
19	worked out either.	09:41
20	And then -- and I'm not familiar with the	09:41
21	data on copper and zinc.	09:41
22	Q. Does the AREDS 2 formulation reduce the	09:41
23	accumulation of lipofuscin pigments?	09:42
24	MR. MILLS: Objection to form.	09:42
25	THE WITNESS: I'm not sure if that has	09:42

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1	been studied.	09:42
2	BY MR. FELDSTEIN:	09:42
3	Q. Are you aware of any mechanism by which	09:42
4	the components of AREDS 2 would be effective to	09:42
5	reduce the accumulation of lipofuscin pigments?	09:42
6	A. Other than what I have already mentioned,	09:42
7	I'm not aware of them, but that's not something	09:42
8	that I have researched.	09:42
9	Q. Do antioxidants reduce the accumulation of	09:42
10	lipofuscin pigments, to your understanding?	09:42
11	A. I don't know that that's been	09:42
12	demonstrated.	09:42
13	Q. Do the pigments that you referred to,	09:42
14	zeaxanthin and lutein, do they reduce the	09:42
15	formation of lipofuscin pigments?	09:42
16	A. Again, I don't -- I think there has been	09:42
17	research in that area, but I'm not familiar with	09:42
18	the papers.	09:42
19	Q. Do you have any further understanding	09:42
20	about the antioxidant biology, on how that treats	09:42
21	dry AMD?	09:43
22	A. So I would be speculating, and I would	09:43
23	prefer not to speculate.	09:43
24	Q. Do you know where in the body the	09:43
25	antioxidant effect needs to be for the formulation	09:43

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1 to be effective for dry AMD? 09:43

2 A. I think that's making a lot of 09:43

3 suppositions, and I think, to some degree, even 09:43

4 the formulation -- I'm not sure how much 09:43

5 experimental basis there has been for all of the 09:43

6 components. 09:43

7 But presumably, it would be in the retina 09:43

8 and the RPE. 09:43

9 Q. You said AREDS formulation was different 09:43

10 than -- excuse me. 09:43

11 You said the AREDS 2 formulation was 09:43

12 different than the AREDS formulation; is that 09:43

13 correct? 09:43

14 A. That is correct. 09:43

15 Q. What was different in AREDS original 09:43

16 playbook? 09:43

17 A. The original AREDS had beta carotene, and 09:43

18 the AREDS 2 has lutein and zeaxanthin. 09:44

19 Q. And do you know why beta carotene was 09:44

20 displaced in the move from AREDS to AREDS 2? 09:44

21 A. My recollection is that in the original 09:44

22 AREDS trial, there was a safety signal of 09:44

23 increased lung cancer in smokers receiving beta 09:44

24 carotene and that they, therefore, switched the 09:44

25 beta carotene out for zeaxanthin and lutein when 09:44

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1	they formulated AREDS 2.	09:45
2	Q. Do you know what the function of beta	09:45
3	carotene was in the AREDS formulation?	09:45
4	A. Well, presumably, to avoid vitamin A	09:45
5	deficiency and to provide a substrate for the	09:45
6	visual cycle.	09:45
7	Q. It was to increase the turnover of the	09:45
8	visual cycle?	09:45
9	A. You know, you're asking me to speculate on	09:45
10	what the authors had in mind, and I would like to	09:45
11	take a minute to read the actual paper. Do you	09:45
12	have an exhibit number?	09:45
13	Q. I do. Let me just -- before you go there,	09:45
14	can I ask just ask you --	09:45
15	A. No, let me just --	09:45
16	Q. -- do you understand the function of beta	09:45
17	carotene in the AREDS formulation?	09:45
18	A. I think I already answered that question.	09:46
19	Q. I'm not asking -- the reason I'm re-asking	09:46
20	the question is you asserted that I was asking you	09:46
21	to speculate. I'm not asking you to speculate.	09:46
22	I'm asking, do you personally understand it?	09:46
23	A. My understanding was that this was a --	09:46
24	this was a clinical trial looking to see whether	09:46
25	supplements that included vitamin A as one	09:46

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1	component, which is feeding, obviously, the visual	09:46
2	cycle, would be beneficial in dry AMD patients.	09:46
3	And they found that AREDS was beneficial	09:46
4	for the subset of dry AMD patients.	09:46
5	So may I -- can we find --	09:46
6	Q. Sure. Take a look at whatever you'd like.	09:46
7	A. -- the paper?	09:46
8	Does anyone have the exhibit number?	09:46
9	Nobody has it?	09:47
10	Q. If you know what paper you're looking for	09:47
11	in --	09:47
12	A. I'm looking for AREDS.	09:47
13	Q. -- your declaration.	09:47
14	It may be 1022, but that's just from	09:47
15	memory.	09:47
16	A. 1022, yeah.	09:47
17	Q. Do you want a question, or do you just	09:47
18	want to read it?	09:47
19	A. Give me a few minutes to read, please.	09:47
20	Q. Okay.	09:47
21	A. So -- oh, okay.	09:47
22	All right.	09:52
23	Q. Having --	09:52
24	A. So --	09:52
25	Q. Can I ask a question so that --	09:52

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1	A. Yes, of course.	09:52
2	Q. -- there's something for you to respond	09:52
3	to?	09:52
4	A. Absolutely.	09:52
5	Q. Having re-reviewed Exhibit 1022, do you	09:52
6	understand what the purpose of beta carotene was	09:52
7	in the AREDS formulation?	09:52
8	A. So there's actually very little in this	09:52
9	paper that's directly relevant to that and	09:52
10	responsive to that, but there is a sentence or two	09:52
11	at the bottom of page 11, where it says (as read):	09:52
12	"Beta carotene, another carotenoid with antioxidant	09:52
13	potential, was included because it was readily	09:52
14	available and under investigation in clinical trials	09:52
15	of heart disease and cancer."	09:52
16	So -- and that's pretty much all it says.	09:52
17	They basically included -- they group it	09:52
18	with vitamin C and vitamin E and call them	09:52
19	antioxidants, so they appear to have thought of it	09:52
20	as an antioxidant.	09:52
21	Q. Rather than substrate to feed the visual	09:52
22	cycle; is that correct?	09:53
23	A. Well, a POSA would recognize that beta	09:53
24	carotene is a substrate for the visual -- or	09:53
25	precursor for the substrates to the visual cycle,	09:53

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1	but this particular reference is silent on that	09:53
2	point.	09:53
3	Q. The AREDS paper, Exhibit 1022, indicates	09:53
4	that beta carotene was used because it had	09:53
5	antioxidant potential; correct? That's the only	09:53
6	function identified?	09:53
7	A. Well, so this was Report Number 8, and	09:53
8	there were seven preceding reports, which may have	09:53
9	gone into more detail on the study design. But in	09:53
10	this particular paper, that's all it says.	09:53
11	Q. And there is a difference between beta	09:53
12	carotene and vitamin A; correct?	09:53
13	A. Well, vitamin A is an inclusive term that	09:53
14	includes retinol, retinal, retinoic acid, retinyl	09:54
15	acetate, and dimers, such as beta carotene and	09:54
16	other -- that's the primary one, but there are	09:54
17	some other related compounds that are also present	09:54
18	in the diet.	09:54
19	Q. Isn't beta carotene a provitamin A?	09:54
20	A. Well, it is -- there's some inconsistency	09:54
21	in the literature, but it is also sometimes	09:54
22	referred as to a provitamin, yes.	09:54
23	Q. And it's not a retinoid; correct?	09:54
24	A. Again, it's a little bit of a semantic	09:54
25	thing. It is a dimer, which is typically -- my	09:54

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1	understanding, it's cleaved in the gut and is a	09:54
2	precursor to the retinoids.	09:54
3	Q. And do you understand the antioxidant	09:54
4	properties of beta carotene? Do you understand	09:54
5	the chemistry of that?	09:54
6	MR. MILLS: Objection. Scope.	09:55
7	THE WITNESS: I have not done reading on	09:55
8	the antioxidant properties of beta carotene.	09:55
9	BY MR. FELDSTEIN:	09:55
10	Q. Do you have an understanding if --	09:55
11	Well, let me -- just as a setup, if I	09:55
12	refer to vitamin A as the retinoids distinct from	09:55
13	beta carotene, is that okay? Can we use that	09:55
14	definition?	09:55
15	A. That's okay.	09:55
16	Q. Okay. Do you have an understanding of	09:55
17	whether the antioxidant properties of beta	09:55
18	carotene differ from vitamin A retinoids?	09:55
19	A. That is not something that I have	09:55
20	researched.	09:55
21	Q. Do you know if that's addressed in the art	09:55
22	anywhere?	09:55
23	A. I'm sorry?	09:55
24	Q. Do you know generally if the art has	09:55
25	considered it, whether beta carotene has different	09:55

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1 antioxidant potential than vitamin A retinoids? 09:55

2 A. I would not be surprised if that has been 09:55

3 researched. 09:55

4 Q. Okay. In terms of beta carotene also 09:55

5 providing vitamin A -- you had mentioned that 09:56

6 earlier; correct? 09:56

7 A. The way you're referring to vitamin A, 09:56

8 yes. 09:56

9 Q. In fact, in AREDS study, Exhibit 1022, 09:56

10 didn't they find that the serum levels of vitamin 09:56

11 A did not increase with treatment? 09:56

12 It's the bottom of page 7, to 8. 09:56

13 A. It's page 7. I see page 7. Give me just 09:56

14 a second. 09:56

15 I'm looking for something else here as 09:56

16 well. 09:56

17 So with the caveat that 57 percent of 09:57

18 AREDS participants were using a multivitamin or at 09:57

19 least one ingredient found in the AREDS 09:57

20 formulation at the time of their AREDS screening 09:57

21 examination, which is on page 10 of the same 09:57

22 paper, the serum levels of vitamin A did not show 09:57

23 a statistically significant increase after 09:57

24 starting AREDS. 09:57

25 Q. And what, if any, is the import of no 09:57

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1	increase in vitamin A after administering beta	09:57
2	carotene?	09:57
3	MR. MILLS: Objection to form and scope.	09:57
4	THE WITNESS: Well, that's an increase in	09:57
5	serum vitamin A levels. And I think it's a piece	09:57
6	of information, and I think there are a number of	09:57
7	possible explanations.	09:57
8	And let me just look. I don't remember	09:57
9	them addressing that in their comments, but let me	09:57
10	look for that.	09:57
11	So they do address -- they do provide one	09:58
12	explanation.	09:58
13	Q. Where are you reading?	09:58
14	A. I'm on the bottom of page 10. It says (as	09:58
15	read):	09:58
16	"Thus, in addition to their dietary intake of	09:58
17	vitamins C and E, beta carotene, and zinc, these	09:58
18	persons had an increase in their intake by	09:58
19	approximately 100 percent of the RDA for each of the	09:58
20	study ingredients whether assigned to placebo or	09:58
21	active intervention."	09:58
22	So this was -- sorry. This was -- I	09:58
23	should back up a sentence. The preceding sentence	09:58
24	says (as read):	09:58
25	"Approximately 67 percent of participants chose to	09:58

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1 take Centrum (about 13 percent of the AREDS 09:58
2 participants who were not taking vitamins at the 09:58
3 start of the study decided to take a multivitamin 09:58
4 along with the study medication, perhaps because they 09:58
5 were enrolling in this long-term study assessing the 09:59
6 effects of vitamins and minerals). Thus, in addition 09:59
7 to their dietary intake of vitamins C and E, beta 09:59
8 carotene, and zinc, these persons had an increase in 09:59
9 their intake by approximately 100 percent of the RDA 09:59
10 for each of the study ingredients whether assigned to 09:59
11 placebo or active intervention. Any increase in 09:59
12 serum levels resulting from this intake was 09:59
13 negligible compared with the serum increases from the 09:59
14 use of the study supplements. The statistical power 09:59
15 of the study to test its primary hypothesis about 09:59
16 high doses of the study ingredients might have been 09:59
17 reduced to the extent that prior use or the continued 09:59
18 use of RDA doses of these ingredients" -- sorry -- 09:59
19 "of these nutrients or other nutrients in the Centrum 10:00
20 formulation affect the risk of AMD development." 10:00
21 I think what they are trying to say is 10:00
22 that these are patients who had dietary intake of 10:00
23 these vitamins, they had in many cases 10:00
24 multivitamins such as Centrum that they were 10:00
25 taking, and they had the AREDS vitamins, and that 10:00

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1	this may have affected the statistical power of	10:00
2	their ability to detect differences, depending on	10:00
3	whether they were taking the study -- study	10:00
4	ingredients or not.	10:00
5	Q. So it's not the case that there's some	10:00
6	limit on how much vitamin A you can get into the	10:00
7	serum --	10:00
8	MR. MILLS: Objection to form and scope.	10:00
9	BY MR. FELDSTEIN:	10:00
10	Q. -- is that true?	10:00
11	A. Say again, please.	10:00
12	Q. Is it not -- is there any limit to how	10:00
13	much vitamin A you can get into the serum?	10:00
14	MR. MILLS: Objection to form and scope,	10:00
15	to the extent it calls for speculation.	10:00
16	THE WITNESS: I don't know the answer to	10:00
17	that.	10:00
18	BY MR. FELDSTEIN:	10:00
19	Q. And earlier, when we were talking about	10:00
20	vitamin A levels, you had particularly noted serum	10:00
21	levels. Are there other levels of vitamin A in	10:01
22	the body that are biologically relevant besides	10:01
23	the serum?	10:01
24	A. Yes. In particular, of course, we're	10:01
25	talking about the retina and the RPE, and we're	10:01

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1 also -- another important organ for vitamin A is 10:01
2 the liver because that is the primary storage 10:01
3 organ for vitamin A. 10:01
4 Q. I think you said earlier -- and it may 10:01
5 have been in the context of AREDS 2 -- that the 10:01
6 individual components had not been separately 10:01
7 evaluated for their effect on macular 10:01
8 degeneration. Did I understand that correctly? 10:01
9 A. So I'm looking at page 10 of this same 10:01
10 reference, 1022, and there is some responsive 10:01
11 information to that, and so I will just read that. 10:01
12 (As read): 10:01
13 "Two other trials assessed supplementation for 10:02
14 patients with AMD. A small randomized trial, 10:02
15 completed before AREDS began, suggested a benefit of 10:02
16 large doses of zinc on visual acuity in persons with 10:02
17 AMD." 10:02
18 Let's see. 10:02
19 (As read): 10:02
20 "Results from another randomized trial reported that 10:02
21 after four years of supplementation, 500 IU per day 10:02
22 of vitamin E had little benefit in reducing the risk 10:02
23 of development or progression of AMD in a population 10:02
24 of 1,193 volunteers." 10:02
25 And there was one other study. I'm going 10:02

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1	to ask your indulgence and let me look through my	10:02
2	report to see if I can find it.	10:02
3	Q. And take your time, but if you want, I can	10:04
4	give you a very specific question.	10:04
5	A. Yeah, just give me a minute, please.	10:04
6	So there were a couple of other papers	10:05
7	that I referenced in my report in paragraph 85,	10:05
8	so -- and I don't know if they will be responsive	10:05
9	to your question because they were for different	10:05
10	conditions.	10:05
11	But Berson discusses vitamin A treatment	10:05
12	for -- vitamin A and vitamin E treatment for	10:05
13	retinitis pigmentosa, and Jacobson taught vitamin	10:05
14	A treatment for Sorsby's fundus dystrophy.	10:05
15	And then there are some other references	10:05
16	talking about vitamin A supplementation for	10:06
17	nonocular disease, but it's all in the report --	10:06
18	in the declaration.	10:06
19	Q. So the question for you, then, is: Are	10:06
20	you aware of any study demonstrating that beta	10:06
21	carotene itself has a treatment effect on AMD?	10:06
22	A. Just a second, please.	10:06
23	I think the answer is no, but let me	10:06
24	caveat by just saying that the AREDS had four	10:06
25	study groups, antioxidants, which was -- so Group	10:06

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1 1 was vitamin C, vitamin E, and beta carotene. 10:06
2 Group 2 was zinc. Group 3 was vitamin A, vitamin 10:06
3 C -- excuse me -- beta carotene, vitamin C and 10:06
4 vitamin E plus zinc. And Number 4 was placebo. 10:06
5 So in AREDS, it was -- the -- the groups 10:07
6 with the antioxidants did better, and the group 10:07
7 that did statistically significantly best was 10:07
8 the -- or showed statistically significant effect 10:07
9 was the antioxidants plus zinc group. But that 10:07
10 did include these other ingredients, so even Group 10:07
11 1 did also include vitamin C and vitamin E. 10:07
12 Q. Right. And just to be clear for others 10:07
13 who are going to read this later, because of the 10:07
14 way AREDS was conducted, there was no way to 10:07
15 separately evaluate whether the beta carotene was 10:07
16 providing the treatment effect or not; correct? 10:07
17 A. That's the way I read this, yes. 10:07
18 Q. And are you aware of any studies that 10:07
19 evaluated the effect of beta carotene on the 10:07
20 treatment of Stargardt's disease? 10:07
21 A. It's not coming to mind at this point. If 10:08
22 it's in my report, I stand by it. 10:08
23 Q. Are you aware of any studies that 10:08
24 evaluated effect of beta carotene on lipofuscin 10:08
25 accumulation? 10:08

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1 A. It's not coming to mind, but if it's in my 10:08
2 report, I stand by it -- in my declaration. 10:08
3 Q. Now, you had said earlier, in effect, that 10:08
4 for Stargardt's patients, the recommendation is to 10:08
5 not take vitamin A supplementation because it 10:09
6 could produce more ATR. Is that roughly correct, 10:09
7 what you said earlier? 10:09
8 MR. MILLS: Objection to form. 10:09
9 THE WITNESS: Well, it could exacerbate 10:09
10 lipofuscin formation rate due to increasing the 10:09
11 concentration -- the already elevated 10:09
12 concentration, potentially, of ATR in the rod 10:09
13 outer segments and/or the RPE. That is my 10:09
14 understanding. 10:09
15 BY MR. FELDSTEIN: 10:09
16 Q. And what I am trying to understand is, if 10:09
17 both Stargardt's disease and dry AMD are 10:09
18 associated with lipofuscin accumulation, why 10:09
19 wouldn't you also counsel AMD patients against 10:09
20 taking additional vitamin A? 10:09
21 A. I think principally because we have the 10:09
22 AREDS study that shows that taking the dosage of 10:10
23 vitamin -- of beta carotene, which I believe was 10:10
24 15 milligrams per day in the AREDS study, was not 10:10
25 harmful and that the antioxidant group and the 10:10

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1 antioxidant plus zinc group, which included that 10:10
2 dosage, showed a beneficial effect given -- agreed 10:10
3 with the caveat that the individual components 10:10
4 were not tested separately. 10:10

5 Q. Besides the AREDS study, Exhibit 1022, are 10:10
6 there other reasons why you don't counsel AMD 10:10
7 patients against taking additional vitamin A? 10:10

8 A. Well, that's the biggest study that we 10:10
9 have, and it's a well-done study, and I am not 10:10
10 aware of any study that indicates that vitamin A 10:10
11 supplements in this type of dose are harmful to 10:10
12 patients with AMD. And we do have the -- you 10:11
13 know, we do have the -- you know, we do have these 10:11
14 studies. 10:11

15 Nowadays, we do recommend the AREDS 2 10:11
16 formulation, but I'm not aware of other reasons 10:11
17 not to -- for them to avoid those -- those 10:11
18 supplements. 10:11

19 Q. But if biologically in a Stargardt's 10:11
20 patient vitamin A supplementation runs the risk of 10:11
21 overdriving the visual cycle and producing more 10:11
22 ATR, biologically wouldn't that also be a concern 10:11
23 for AMD patients? 10:11

24 MR. MILLS: Objection to form. 10:11

25 THE WITNESS: So, again, these are very -- 10:11

1 the accumulation of lipofuscin is much slower in 10:11
2 AMD. It's occurring over decades. 10:11
3 And we haven't discussed it in detail, but 10:11
4 having too little vitamin A is also deleterious in 10:12
5 the sense that it can impair night vision. 10:12
6 And so there is a balance there, and I 10:12
7 think that where you set that balance is different 10:12
8 for a Stargardt's patient and an AMD patient. 10:12
9 BY MR. FELDSTEIN: 10:12
10 Q. Let's try to simplify a little bit and 10:12
11 assume that all the patients in this question have 10:12
12 a healthy level of vitamin A already. It's the 10:12
13 case that for Stargardt's, you would recommend 10:12
14 against additional vitamin A; correct? 10:12
15 A. That is correct. 10:12
16 Q. And for the AMD patient who has a healthy 10:12
17 level of vitamin A, for the same reasons as 10:12
18 Stargardt, wouldn't it also make sense to 10:12
19 recommend for the healthy AMD patient against 10:12
20 additional vitamin A so as not to overproduce ADR? 10:12
21 A. I think that's a theoretical concern, and 10:13
22 I have not seen any experimental data to validate 10:13
23 it. 10:13
24 From a practical standpoint, we typically 10:13
25 recommend the AREDS formulation which contains 10:13

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1 zeaxanthin and lutein rather than beta carotene or 10:13
2 vitamin A, and I do not recommend additional 10:13
3 supplements for my AREDS patients other than I'm 10:13
4 fine with them taking a Centrum Silver for general 10:13
5 health reasons. 10:13
6 Q. And roughly how many dry AMD patients do 10:13
7 you see in a given year? 10:13
8 A. In a year? Hundreds. Maybe a thousand or 10:13
9 two. 10:13
10 MR. MILLS: Are we ready for a break? 10:13
11 MR. FELDSTEIN: That's fine. 10:13
12 MR. MILLS: We have been going about an 10:13
13 hour. 10:13
14 MR. FELDSTEIN: Off the record, please. 10:13
15 (Recess taken.) 10:26
16 MR. FELDSTEIN: Back on the record. 10:26
17 BY MR. FELDSTEIN: 10:26
18 Q. I want to switch topics, but one follow-up 10:26
19 from earlier. Beta carotene versus vitamin A, do 10:26
20 you have any understanding of whether they are 10:26
21 transported in the body the same or differently? 10:26
22 A. You know, I address -- I think what's in 10:26
23 my report that addresses that most directly is 10:27
24 where I describe that there is an enzyme in the 10:27
25 gut, in the small intestine, beta carotene 10:27

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1	dioxygenase, which basically converts beta	10:27
2	carotene into retinal, and that's -- I don't think	10:27
3	I have a further understanding of the transport	10:27
4	processes in the body beyond that.	10:27
5	Q. Do you know if retinal and beta carotene	10:27
6	are both transported into the retina?	10:27
7	A. I don't know that for sure.	10:28
8	Q. Do you know if any of the AREDS 2	10:28
9	components are transported into the retina?	10:28
10	A. I know that the macular area contains high	10:28
11	concentrations of zeaxanthin and lutein, if that's	10:28
12	what you're referring to. And the precise	10:28
13	biochemistry of those, how and where they're	10:28
14	synthesized and transported, I don't have detailed	10:28
15	knowledge of.	10:28
16	Q. Leaving aside beta carotene, do you have	10:28
17	an understanding if any of the other components of	10:28
18	the original AREDS formulation are transported	10:28
19	into the retina?	10:28
20	A. I think there's an assumption that that's	10:28
21	the case because the whole point of the AREDS	10:28
22	studies was to assess the response of a macular or	10:28
23	retinal disease to these formulations.	10:28
24	Beyond that, I don't have a detailed	10:28
25	knowledge of how these various nutrients get into	10:28

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1 the retina beyond the -- you know, zinc and copper 10:29
2 presumably have ion channels that are involved in 10:29
3 their transport, which is the general mechanism 10:29
4 for minerals. 10:29
5 Q. Switching a little bit. You had mentioned 10:29
6 that you have seen less than 10 Stargardt's 10:29
7 patients over the past 31 years; is that correct? 10:29
8 A. That's an estimate, yeah. Might be a 10:29
9 little more, but it's not a large number. 10:29
10 Q. And what's the magnitude, would you say, 10:29
11 of the number of patients in total you've seen 10:29
12 over that time period, roughly? 10:29
13 A. You know, I can't give you -- it's hard to 10:29
14 give you an estimate. I'll say that I see about 10:29
15 150 patients a week, and of course, many of them 10:29
16 are seen more than once. We have a lot of 10:29
17 patients on a twice-a-year schedule, and we have 10:29
18 some that we see more frequently. So you can 10:29
19 extrapolate from that. I have been in practice 10:29
20 for a little over 30 years. 10:30
21 Q. Okay. Thousands of patients, at least, 10:30
22 over 30 years? 10:30
23 A. Many thousands. 10:30
24 Q. And if there's no treatment for 10:30
25 Stargardt's, what happens to a Stargardt's disease 10:30

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1	subject?	10:30
2	A. So there is a variety of -- there's a	10:30
3	spectrum of presentations. Many of these patients	10:30
4	present with vision loss in childhood or young	10:30
5	adulthood. Some present in middle age.	10:30
6	From a practical standpoint in terms of my	10:30
7	interactions with them, typically, I will make	10:30
8	either a presumptive -- nowadays, with genetic	10:30
9	testing, I will make a presumptive diagnosis and	10:30
10	then typically refer them to Dr. Duncan at UCSF	10:30
11	for genetic testing and her expert evaluation	10:30
12	because she sees many more patients with this rare	10:30
13	disease and other rare macular diseases than	10:30
14	anyone else in the area.	10:31
15	And she's also plugged into the various	10:31
16	research studies. So sometimes she will enter	10:31
17	them into research studies. And then we'll give	10:31
18	them the lifestyle counseling that we discussed.	10:31
19	And in terms of -- you said "what happens	10:31
20	to them," which is a very broad question. Most of	10:31
21	these patients do have significant impacts on	10:31
22	their lives based on the fact that they don't see	10:31
23	well.	10:31
24	And some of them -- many of them will end	10:31
25	up functionally blind at some point in their	10:31

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1	lives. And so, of course, they have major	10:31
2	adjustment that they make. Some will work, and	10:31
3	some will not. There's a wide variety.	10:31
4	Q. Have you told children, based on a	10:31
5	preliminary diagnosis of Stargardt's disease, that	10:31
6	the expectation is that they'll become	10:31
7	functionally blind?	10:31
8	A. So I see adults in my practice. I don't	10:31
9	see patients under 18. So I have not had that	10:31
10	personal experience. And I don't recall a	10:31
11	specific patient during training who fit that	10:32
12	profile.	10:32
13	Q. And do you tell young adult patients that	10:32
14	you've preliminarily diagnosed with Stargardt's	10:32
15	disease that the expectation is that they will	10:32
16	become functionally blind?	10:32
17	A. So typically, once I see them, I make a	10:32
18	presumptive diagnosis. I explain to them that	10:32
19	they have a potentially serious macular condition	10:32
20	and that I am referring them to Dr. Duncan, who is	10:32
21	much more -- you know, sees many more of these	10:32
22	patients than anyone else and can give them more	10:32
23	detailed information about their -- the natural	10:32
24	history and prognosis for their particular case.	10:32
25	As I mentioned, there is a spectrum.	10:32

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1	Q. So you don't provide any information to	10:32
2	young adult patients on prognosis when you	10:32
3	presumptively identify Stargardt's disease?	10:32
4	A. Typically, again, I've only seen these	10:32
5	patients once or twice and then making that	10:32
6	referral. And typically, I will tell them that	10:33
7	they appear to have a macular dystrophy, that it	10:33
8	may well be Stargardt's, or it may be a different	10:33
9	dystrophy because there are many dystrophies, and	10:33
10	sometimes the final diagnosis nowadays is made	10:33
11	genetically.	10:33
12	And I will -- you know, if they -- my	10:33
13	primary focus is on getting them referred to UCSF,	10:33
14	and I don't know -- I certainly don't sugarcoat	10:33
15	it, but I'm typically not going to be giving them	10:33
16	a detailed prognosis on the basis of one or two	10:33
17	visits and no genetic testing. I'm usually going	10:33
18	to defer that.	10:33
19	Now, if they ask me, "Well, if this is	10:33
20	Stargardt's, what's the prognosis," I'll tell them	10:33
21	we don't have an effective treatment at this time	10:33
22	and it's a progressive disease and there's a	10:33
23	variety of -- you know, there is a variation or a	10:33
24	spectrum of progression rates and final outcomes	10:34
25	but, you know, it's not going to go away and it's	10:34

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1 going to have significant impact on their life. 10:34

2 Most of them kind of know that already. 10:34

3 But that's -- that's the nature of the 10:34

4 conversation. 10:34

5 It would be inappropriate for me to give 10:34

6 them -- to attempt to give them a detailed 10:34

7 prognosis given the fact that, you know, usually 10:34

8 we don't have a definitive diagnosis yet because 10:34

9 they haven't had the genetic testing. They 10:34

10 typically haven't had some of the other detailed 10:34

11 studies that these patients may undergo, including 10:34

12 electrophysiologic testing of the retina. And 10:34

13 given -- you know, just given the fact that the 10:34

14 diagnosis is typically preliminary and that there 10:34

15 is a spectrum of severity and progression rates. 10:34

16 Q. And I will really switch topics now. 10:34

17 Can you turn to paragraph 50 in your 10:34

18 declaration, Exhibit 1004. In the first sentence, 10:35

19 and I'm only going to read up to the colon, you 10:35

20 say (as read): 10:35

21 "As I will explain in detail below, and relying where 10:35

22 appropriate on the opinions of Dr. Guengerich:" 10:35

23 Then you have the summary of your 10:35

24 opinions; correct? 10:35

25 A. Correct. 10:35

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1	Q. At a high level, what are you relying on	10:35
2	Dr. Guengerich for?	10:35
3	A. Well, Dr. Guengerich is an experienced	10:35
4	chemist, and he has detailed knowledge of reaction	10:35
5	mechanisms, common synthetic pathways, you know,	10:35
6	pharmacokinetics and reaction kinetics, molecular	10:35
7	analysis techniques, and other issues that he	10:35
8	deals with on a daily basis that I do not.	10:35
9	So areas that fall into that, the realm of	10:36
10	knowledge of a chemist and related disciplines are	10:36
11	areas -- even though I have some background,	10:36
12	obviously, I have a master's in molecular	10:36
13	biophysics and chemistry, I have a Ph.D. in	10:36
14	microbiology and immunology, which included	10:36
15	coursework in biochemistry, and I use biochemical	10:36
16	techniques in my research in the lab, nonetheless,	10:36
17	this is not something that I do anymore, and it's	10:36
18	not something that I'm exposed to on a daily	10:36
19	basis, nor do I -- nor have I ever had the	10:36
20	detailed knowledge of organic chemistry that he	10:36
21	has.	10:36
22	Q. Okay. I'm going to turn a couple times to	10:36
23	where you refer to him specifically. And I'm	10:36
24	going to basically ask the same question, but I'd	10:36
25	like to know -- I'm just trying to get the line	10:36

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1 between where you have independent opinions and 10:37
2 where you're relying on Dr. Guengerich, given what 10:37
3 you just said about you have some of your own 10:37
4 background. 10:37
5 And so if I could turn you to 10:37
6 paragraph 52. I'm just going to start the 10:37
7 sentence (as read): 10:37
8 "As I discuss in detail below, and relying on the 10:37
9 opinions of Dr. Guengerich where appropriate, it was 10:37
10 known as of the priority date that" and then you have 10:37
11 (i) through (vi). 10:37
12 Can you tell me which of those are your 10:37
13 own independent opinion and which of those are 10:37
14 based on Dr. Guengerich? 10:37
15 A. (i) is my opinion. (ii) is my opinion. 10:37
16 (iii) is his opinion. I've read -- I've read some 10:38
17 of the papers that discuss that, but this is -- 10:38
18 I'm relying on his opinion on this -- primarily on 10:38
19 this point. 10:38
20 Q. I'm sorry. Point (iii)? 10:38
21 A. Uh-huh, yes. 10:38
22 (iv) is my opinion. 10:38
23 (v) is my opinion. 10:38
24 (vi) I would say is say mixture because I 10:38
25 -- he has experience, personal direct experience 10:38

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1	in this field, and I only have what I can read	10:38
2	from literature.	10:38
3	Q. Independent of Dr. Guengerich and things	10:39
4	that you have read specifically for this case, in	10:39
5	terms of point number (vi), "Deuteration of an	10:39
6	existing compound was a known method of creating	10:39
7	improved compounds," what compounds were you aware	10:39
8	of where that had been done?	10:39
9	A. Well, I'm aware that there is a drug --	10:39
10	and I don't know a lot about it, but I'm aware	10:39
11	there is a deuterated drug that's available for	10:39
12	Huntington's chorea, c-h-o-r-e-a.	10:39
13	Q. Do you know the name of it?	10:39
14	A. I don't.	10:39
15	Q. Are there any other -- aside from what you	10:39
16	are relying on from Dr. Guengerich or read	10:40
17	specifically for this case, beyond that one drug,	10:40
18	are there other existing compounds where you know	10:40
19	deuteration was used to create improved compounds?	10:40
20	A. What I would say is I'm aware that this is	10:40
21	an area of research, and I was aware of that	10:40
22	before I read that papers that I cite in my	10:40
23	report, but I can't -- I mean, I -- I'm not aware	10:40
24	of any other approved products or specific	10:40
25	products that are in testing. I'm just aware of	10:40

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1	it as a concept.	10:40
2	Q. And in terms of the treatment for the	10:40
3	Huntington's disease, what was the improvement	10:40
4	that deuteration provided?	10:40
5	A. I would have to speculate. I don't know	10:40
6	for sure.	10:40
7	Q. As of the time period of 2007-2008, to	10:40
8	your knowledge, were there any existing	10:41
9	pharmaceutical compounds where it was known that	10:41
10	they had been improved by deuteration?	10:41
11	MR. MILLS: Objection to form.	10:41
12	THE WITNESS: I'm not sure exactly what	10:41
13	you're -- to the best of my knowledge, none that	10:41
14	had been FDA approved, but there had been research	10:41
15	on such compounds.	10:41
16	BY MR. FELDSTEIN:	10:41
17	Q. Okay. And the research was directed at	10:41
18	creating what types of improvements?	10:41
19	A. Let me refer to the article that I cite.	10:41
20	So there were three studies -- three	10:44
21	articles that I cited in my report, 1046, 1047,	10:44
22	and 1048. And it's a long list, so let me just	10:44
23	summarize.	10:44
24	Many of the effects of deuteration in	10:44
25	terms of therapeutics, not talking about use in	10:44

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1 dilution studies, metabolism studies, but 10:44
2 therapeutics, have to do with slowing metabolic -- 10:44
3 slowing metabolism or elimination of the 10:44
4 therapeutic compounds. 10:44
5 So Kushner, in 1046, K-u-s-h-n-e-r, 10:44
6 discusses a number of potential uses of deuterated 10:44
7 drugs. 10:44
8 Again, these are summary statements. We 10:44
9 can go into more detail if you want to, but in the 10:45
10 abstract they say (as read): 10:45
11 "Most" -- i.e., most of these deuterated 10:45
12 therapeutics -- "are more resistant to metabolic 10:45
13 changes, especially those changes mediated by 10:45
14 cytochrome P450 systems. Deuteration may also change 10:45
15 the pathway of drug metabolism, which may lead to 10:45
16 increased duration of action and lower toxicity." 10:45
17 They mention that (as read): 10:45
18 "Deuteration can lower the genotoxicity of tamoxifen 10:45
19 and other compounds." 10:45
20 And then -- 10:45
21 Q. Can we do just one reference at a time? 10:45
22 A. Sure. If you want me to go into detail, I 10:45
23 want read the whole thing. 10:46
24 Q. Sure. So in Kushner, Exhibit 1046, what's 10:46
25 the closest example of deuteration they give to 10:46

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1	what's proposed by your side in this case to use	10:46
2	C20-deuterated retinoids?	10:46
3	MR. MILLS: Objection. Form. Incomplete	10:46
4	hypothetical. Calls for speculation.	10:46
5	THE WITNESS: So I'm not sure this is an	10:47
6	exhaustive list, and in some cases little detail	10:47
7	is given.	10:47
8	But they mention on page 83 (as read):	10:47
9	"Deuterated analogs of the neurotoxin MPTP" -- I'm	10:47
10	going to omit the chemical name -- "which is oxidized	10:48
11	to more toxic species were prepared to study the	10:48
12	pathway that leads to these changes."	10:48
13	That's all it says, with a reference.	10:48
14	And then in the same section, on page 84,	10:48
15	it states (as read):	10:48
16	"The metabolic products of many drugs are toxic, and	10:48
17	deuteration can lower such toxicity by reducing	10:48
18	metabolism."	10:48
19	And they go through -- they discuss	10:48
20	halogenated anesthetics, chloroform, sevoflurane.	10:48
21	And then they mention (as read):	10:48
22	"Deuteration reduces toxicity of butylated	10:48
23	hydroxytoluene, an antioxidant, and reduces the	10:48
24	toxicity of diethyl hydroxy adipate, which is a	10:49
25	potential food toxin."	10:49

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1	They also discuss the deuteration of	10:49
2	tamoxifen, which they report has lower	10:49
3	genotoxicity than the normal hydrogenated form.	10:49
4	And I think those are probably the most	10:49
5	responsive to your question.	10:49
6	Q. So I had asked for you to identify the	10:49
7	closest example of deuteration in Kushner. Am I	10:49
8	to take it from your answer that all those answers	10:49
9	you gave are equally close to the proposed C20	10:49
10	deuteration of retinoids here?	10:49
11	MR. MILLS: Objection to form. Misstates	10:50
12	the testimony.	10:50
13	THE WITNESS: What I would say is that all	10:50
14	of these represent areas of research or results	10:50
15	where deuteration may -- may lead to decreased	10:50
16	toxicity or reduced rates of formation of a toxic	10:50
17	byproduct. As for ranking those, I don't have	10:50
18	enough information to do that.	10:50
19	BY MR. FELDSTEIN:	10:50
20	Q. Are there any that, from the information	10:50
21	you do have or your general experience, that you	10:50
22	can identify as having a mechanism similar to	10:50
23	what's being proposed here for the C20 deuteration	10:50
24	of retinoids?	10:50
25	MR. MILLS: Objection to form. Scope. To	10:50

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1 the extent it calls for speculation. 10:50

2 BY MR. FELDSTEIN: 10:50

3 Q. I'm going to redo the question. 10:50

4 Are there any of the examples you 10:50

5 identified in Kushner that you can identify as 10:50

6 having -- the deuteration having a mechanism 10:51

7 similar to what's being proposed here for the C20 10:51

8 deuteration of retinoids? 10:51

9 MR. MILLS: Objection to form. Scope. 10:51

10 Calls for speculation. 10:51

11 THE WITNESS: To some degree, we're 10:51

12 getting into Dr. Guengerich's area of expertise. 10:51

13 I think if you read the paper as a whole and the 10:51

14 concept of the kinetic isotopic effect is common 10:51

15 to all of what we're discussing in this paper and 10:51

16 has to do with, in general, barriers to cleavage 10:51

17 of a carbon-hydrogen bond, and the details of 10:51

18 which I defer to Dr. Guengerich. 10:51

19 In terms of the specific information that 10:51

20 they provide, the only information they provide on 10:51

21 MPTP is the deuteration would be targeted toward 10:51

22 reducing oxidation, which is, my understanding, my 10:51

23 limited understanding, relying on Dr. Guengerich, 10:52

24 a different mechanism in terms of the, you know, 10:52

25 actual details of the molecular mechanism than 10:52

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1 what were -- what's addressed in the patent. 10:52

2 And then as for the other compounds that 10:52

3 are discussed here -- give me a moment. 10:52

4 I would actually -- with reference to the 10:52

5 | previous point, there is a sentence on 83 that 10:52

6 | sort of sums up what I was trying to say, which is 10:52

7	(as read):	10:52
---	------------	-------

8 "One of the key steps in all such reactions" -- 10:52

9 having to do with in this case drug metabolism -- "is 10:52

10 the breaking of a C-H bond. And compounds that have 10:52

11	C-D structures at the cite of enzymatic attack are	10:52
----	--	-------

12 more resistant to P450 change." 10:52

13 BY MR. FELDSTEIN: 10:53

14	Q. In your --	10:53
----	---------------	-------

15	A. Wait, wait, wait.	10:53
----	----------------------	-------

16	Q. I just want to ask you --	10:53
----	------------------------------	-------

17	A. I'm not done. I'm on page 83, right	10:53
----	--	-------

18	column, halfway down the page.	10:53
----	--------------------------------	-------

19	(As read):	10:53
----	------------	-------

20 "So the mechanism for the reducing the toxicity of 10:53

21 halogenated anesthetics appears to be related to 10:53

22 | reducing the release of inorganic fluorine in the 10:53

23	cytochrome P450 system. The tamoxifen toxicity is	10:53
----	---	-------

24 thought to be related to hydroxylation of the 10:54

25	tamoxifen molecule, converting to a DNA adduct."	10:54
----	--	-------

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1 So these are, at the molecular level, 10:54
2 different mechanisms from what's happening in the 10:54
3 reactions that are discussed in the patent. 10:54
4 Q. You pointed to Exhibit 1046 Kushner 10:54
5 page 83, right-hand column, halfway down about C-H 10:54
6 bond. Is it your understanding that any reaction 10:54
7 having a C-H bond breaking is amenable to 10:54
8 improvement by replacing it with deuterium? 10:54
9 MR. MILLS: Objection to form, scope, and 10:54
10 to the extent it calls for speculation. 10:54
11 THE WITNESS: You said "any," which means 10:54
12 a hundred percent of the time. 10:54
13 First of all, this exceeds my area of 10:54
14 knowledge, and I would defer to Dr. Guengerich. 10:54
15 And so the answer -- the real answer is, I don't 10:54
16 know if there are exceptions, and I would defer to 10:55
17 Dr. Guengerich. 10:55
18 BY MR. FELDSTEIN: 10:55
19 Q. And when you answer in terms of 10:55
20 exceptions, is it your expectation that, in 10:55
21 general, any reaction having a C-H bond breaking 10:55
22 is amenable to improvement by replacing it with 10:55
23 deuterium? 10:55
24 MR. MILLS: Objection to form, scope, and 10:55
25 to the extent it calls for speculation. Asked and 10:55

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1	answered.	10:55
2	THE WITNESS: It seems like the same	10:55
3	question except maybe you're lowering the	10:55
4	threshold a little bit from a hundred percent.	10:55
5	I would say again, this exceeds my level	10:55
6	of knowledge. This is a question where I would	10:55
7	defer to Dr. Guengerich, and I don't know the	10:55
8	answer to your question.	10:55
9	BY MR. FELDSTEIN:	10:55
10	Q. Okay. Did you want to move on to the next	10:55
11	exhibit, 1047, you identified? And just so --	10:55
12	give you a heads up, I'm going to be basically	10:55
13	asking the same thing about analogous disclosures.	10:55
14	A. If you will give me a moment to read,	10:55
15	please.	10:55
16	Q. Sure, take your time. Just to be clear,	10:56
17	you're looking at 1047, Blake?	10:56
18	A. Yes.	10:56
19	So this is -- they go through a number of	11:01
20	different compounds, but for the most part, I did	11:01
21	not identify -- well, I did not identify anywhere	11:01
22	that specifically used deuteration to reduce	11:01
23	toxicity.	11:01
24	They were primarily interested in the	11:01
25	effect of deuteration on the pharmacological	11:01

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1	effect of various agents and on the rates of	11:01
2	metabolism.	11:01
3	Q. And so just so that your answer is in	11:01
4	response to a question, I'm going to ask the	11:01
5	question, if I can; otherwise, the record won't	11:01
6	read clearly.	11:01
7	My question is, in Exhibit 1047, Blake,	11:01
8	can you identify any examples where the	11:02
9	deuteration had a similar mechanism to what's	11:02
10	being proposed here for the C20 deuteration of	11:02
11	retinoids?	11:02
12	MR. MILLS: Objections to form, scope, and	11:02
13	speculation.	11:02
14	THE WITNESS: So in the broadest sense,	11:02
15	yes. For example, barbiturates that were	11:02
16	deuterated had decreased metabolism rates.	11:02
17	In a narrower sense, no, because what they	11:02
18	were looking for was trying to reduce metabolism	11:02
19	rates in order to prolong the lifetime of an	11:02
20	exogenous pharmaceutical in the body, whereas the	11:03
21	goal of the invention in the patents-in-suit is	11:03
22	primarily to reduce a harmful metabolic pathway	11:03
23	involving development of precursors to lipofuscin.	11:03
24	So it sort of depends on how you look at it.	11:03
25	BY MR. FELDSTEIN:	11:03

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1	Q. Are you looking at the formation of	11:03
2	lipofuscin pigments from ATR as a metabolic	11:03
3	process?	11:03
4	A. Again, it depends on how you look at it	11:03
5	and how you define it. So from the broader	11:03
6	perspective, in both of these situations,	11:03
7	deuteration is slowing an undesirable reaction;	11:03
8	however, the nature of the undesirable reaction is	11:03
9	different.	11:03
10	With barbiturates, the undesirable	11:03
11	reaction is not really that undesirable; it's	11:03
12	clearance of the drug from the body.	11:03
13	Whereas in the case of macular	11:03
14	degeneration and these other dystrophies that	11:04
15	we're talking about, the undesirable reaction is	11:04
16	formation of non-metabolic -- of toxic byproducts	11:04
17	that cannot be metabolized.	11:04
18	Q. I may not have been clear. I'm going to	11:04
19	back up a question for foundation.	11:04
20	Is it your view that every chemical	11:04
21	reaction that occurs within the body is a	11:04
22	metabolic process?	11:04
23	MR. MILLS: Objection to form. Scope.	11:04
24	THE WITNESS: I think that's a semantic	11:04
25	question. It really depends on how you define it.	11:04

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1	I think -- certainly, we're not talking about a	11:04
2	desirable metabolic process. We're talking about	11:04
3	a harmful process when we're talking about	11:04
4	formation of these lipofuscin precursors.	11:04
5	Is drug clearance a metabolic process?	11:04
6	These drugs, for the most part, are -- most drugs	11:05
7	are not found in nature. So is it normal	11:05
8	metabolism? Again, this is semantics. I think	11:05
9	most people would say that's a metabolic process.	11:05
10	BY MR. FELDSTEIN:	11:05
11	Q. I'm just asking for your opinion here to	11:05
12	get it clear on the record. And maybe it's	11:05
13	semantic, but I'm just trying to get your opinion.	11:05
14	I'll break it down a little bit further.	11:05
15	You're very familiar with the visual	11:05
16	cycle; correct?	11:05
17	A. Yeah.	11:05
18	Q. Do you consider that to be a metabolic	11:05
19	process?	11:05
20	A. Yes.	11:05
21	Q. You're very familiar with the biosynthetic	11:05
22	pathway where ATR is converted into lipofuscin	11:05
23	pigments; correct?	11:05
24	A. Yes.	11:05
25	Q. Do you consider that to be a metabolic	11:05

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1	process?	11:05
2	MR. MILLS: Objection. Form. Scope.	11:05
3	THE WITNESS: I think it depends on how	11:05
4	you would define it semantically. And I'm not	11:05
5	prepared to generate a new opinion on that on the	11:05
6	fly.	11:05
7	BY MR. FELDSTEIN:	11:05
8	Q. Sitting here, you don't have an opinion on	11:05
9	whether the biological -- the biosynthetic pathway	11:05
10	in, for example, Mata Figure 5, Exhibit 1010 is	11:05
11	metabolism or not?	11:06
12	A. Let's go to that figure. You're calling	11:06
13	it a biosynthetic pathway. I think that would	11:06
14	even be a question of whether that's -- they do	11:06
15	call it biosynthesis.	11:06
16	I think these are really semantic	11:06
17	questions. I think the answer really depends on	11:06
18	how you define the word "metabolic." It's not	11:06
19	something -- it's not an opinion that I have	11:06
20	developed. It's -- I think we all agree it's a	11:06
21	deleterious pathway that results in pathology.	11:06
22	So are pathologic pathways metabolic? I	11:06
23	think you can probably find some people who say	11:06
24	yes and some who say no, and it's not a	11:06
25	philosophical question that I've researched or	11:06

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1 that I've prepared to create a new opinion on. 11:06

2 Q. That's all I'm trying to clarify is 11:07

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3 | whether you have an opinion or not. 11:07
```

4 And so the question is, you don't have an 11:07

5 | opinion one way or another on whether the process 11:07

6 depicted in Mata Figure 5 is or is not a metabolic 11:07

```
7 process; is that correct? 11:07
```

8	MR. MILLS: Objection to form. Misstates	11:07
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9 the testimony. Asked and answered. 11:07

10	THE WITNESS: It's not that I don't have	11:07
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11      an opinion on this process.  I have an opinion      11:07
```

```
12      that this is a process that is -- that occurs in      11:07
```

13 various disease states in the macula, that is 11:07

14	harmful, whose occurrence, you know, ideally it	11:07
----	---	-------

15 would be beneficial to minimize. 11:07

16	Whether you consider it metabolic or not	11:07
----	--	-------

17 would depend on whether your definition of 11:07

18	"metabolic" includes pathologic processes as well	11:07
----	---	-------

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19 |         as normal ones.                                     11:07
```

20 So I think it's a semantic difference, and 11:07

21 I'm not prepared to generate a new opinion on the 11:08

```
22      definition of "metabolic" as we sit here on the      11:08
```

23	fly.	11:08
----	------	-------

24	BY MR. FELDSTEIN:	11:08
----	-------------------	-------

25	Q. Do you want to move on to Exhibit 1048?	11:08
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1	You can review it, and then the question is going	11:08
2	to be, can you identify any examples in	11:08
3	Exhibit 1048 where the deuteration used a	11:08
4	mechanism analogous to what's proposed for C20	11:08
5	deuteration of retinoids here?	11:08
6	MR. MILLS: Objections to form, scope, and	11:08
7	to the extent it calls for speculation.	11:08
8	THE WITNESS: So this reference describes	11:10
9	the effects of various degrees of deuteration on	11:10
10	the metabolism of various halogenated anesthetics	11:10
11	in the rat, and the premise of the experiment is	11:10
12	to reduce toxicity because, as they state (as	11:11
13	read):	11:11
14	"Hepatotoxicity and nephrotoxicity may be related to	11:11
15	the metabolism of volatile anesthetics. It would	11:11
16	appear beneficial to decrease the metabolism of these	11:11
17	drugs and thus lessen the amount of unwanted	11:11
18	metabolic products."	11:11
19	So first of all, I defer to Dr. Guengerich	11:11
20	with regard to mechanisms of these reactions. But	11:11
21	at the broadest level, this is an example of	11:11
22	attempting to decrease a -- in this case, a	11:11
23	metabolic pathway that clears the drugs from the	11:11
24	body and reduce the amount of unwanted metabolic	11:11
25	products.	11:11

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1 In that sense, it is analogous to -- at 11:11
2 the highest level, to the invention in the 11:11
3 patents-in-suit. 11:11
4 At a more detailed level, the molecular 11:11
5 mechanisms that they outline in Figure 1 of this 11:12
6 reference, Number 1048, by McCarty, it appears to 11:12
7 me, as a non-chemist, to be a different mechanism 11:12
8 from what is outlined in the system that we are 11:12
9 discussing today, in terms of the molecular 11:12
10 details. Although again, I would defer to 11:12
11 Dr. Guengerich. 11:12
12 BY MR. FELDSTEIN: 11:12
13 Q. And Exhibit 1048 is based on 11:12
14 enzyme-mediated metabolism; correct? 11:12
15 MR. MILLS: Objection. Form. 11:12
16 THE WITNESS: I would defer to 11:13
17 Dr. Guengerich on that question. In my reading of 11:13
18 this -- and if I've missed it, you can point it 11:13
19 out -- I didn't see a specific reference to 11:13
20 enzymatic catalysis of the metabolic scheme that 11:13
21 they propose. 11:13
22 BY MR. FELDSTEIN: 11:13
23 Q. To your understanding, is there any 11:13
24 difference in the effect of deuteration on slowing 11:13
25 a reaction, whether the reaction is 11:13

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1 enzyme-mediated or not? 11:13

2 MR. MILLS: Objections to form, scope, and 11:13

3 to the extent it calls for speculation. 11:13

4 THE WITNESS: I don't know the answer to 11:13

5 that question, and I would defer to 11:13

6 Dr. Guengerich. I'll just leave it at that. 11:13

7 How are we doing on time? 11:14

8 MR. MILLS: It's 11:14. 11:14

9 THE WITNESS: Take a break in ten? 11:14

10 MR. FELDSTEIN: Sure, whenever you like. 11:14

11 BY MR. FELDSTEIN: 11:14

12 Q. Can we turn back to your declaration, 11:14

13 Exhibit 1004, please. 11:14

14 And again, trying to distinguish your 11:14

15 opinions from Dr. Guengerich's opinions. In 11:14

16 paragraph 143, you refer to (as read): 11:14

17 "As discussed in the declaration of Dr. Guengerich, a 11:14

18 chemist of ordinary skill would have recognized that 11:14

19 C20" -- 11:14

20 A. I'm sorry. Am I in the right place? 11:14

21 Q. Paragraph 143. 11:14

22 A. Paragraph 143 of 1004? 11:14

23 Q. Right. About halfway down. 11:14

24 A. "As discussed above"? 11:15

25 Q. "As discussed in the declaration of 11:15

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1	Dr. Guengerich."	11:15
2	MR. MILLS: Are you guys on the same case?	11:15
3	THE WITNESS: I'm not sure we're on the	11:15
4	same piece of paper.	11:15
5	MR. FELDSTEIN: So I'm in Exhibit 1004	11:15
6	from your declaration in IPR 2024-00313.	11:15
7	THE WITNESS: Okay. Well, that's not	11:15
8	Exhibit 1004. If it is, it's in a different --	11:15
9	it's in the other case. I was on the other	11:15
10	declaration.	11:15
11	So let me turn to the appropriate	11:15
12	paragraph. You said 143?	11:15
13	BY MR. FELDSTEIN:	11:15
14	Q. Correct.	11:15
15	A. I'm sorry. Where are we starting?	11:15
16	Q. Six lines down on the right, "As discussed	11:15
17	in declaration of Dr. Guengerich."	11:15
18	A. I see that.	11:15
19	Q. You refer to what a chemist of ordinary	11:15
20	skill would have recognized; correct?	11:15
21	A. I see that.	11:15
22	Q. Do you have any independent expertise for	11:15
23	this statement beyond your reliance on the	11:15
24	declaration of Dr. Guengerich?	11:15
25	A. I do not.	11:15

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1 Q. Continuing in the same paragraph to the 11:16
2 next page, page 71 of Exhibit 1004, you say (as 11:16
3 read): 11:16
4 "In my opinion, and relying on" the declaration" -- 11:16
5 Excuse me. I'm going to read it again. 11:16
6 Paragraph 143, page 71 of Exhibit 1004, 11:16
7 you say (as read): 11:16
8 "In my opinion, and relying on Dr. Guengerich's 11:16
9 analysis of the kinetic isotope effect, a person of 11:16
10 ordinary skill in the art would have had good reason 11:16
11 to employ C20-deuterated vitamin A." 11:16
12 Then it continues. 11:16
13 A. I see that. 11:16
14 Q. Do you have any independent expertise for 11:16
15 this statement beyond your reliance on the 11:16
16 declaration of Dr. Guengerich? 11:16
17 MR. MILLS: Objection to form. 11:16
18 THE WITNESS: Yes. 11:16
19 BY MR. FELDSTEIN: 11:16
20 Q. What's your independent expertise beyond 11:16
21 Dr. Guengerich for this statement? 11:16
22 A. As a clinician who treats patients with 11:16
23 age-related macular degeneration and related 11:17
24 dystrophies, I'm aware that lipofuscin formation 11:17
25 is undesirable and is part of the pathophysiology 11:17

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1 of these diseases, and that it would therefore be 11:17
2 a reasonable therapeutic approach to employ 11:17
3 C20-deuterated vitamin A, based on the chemistry as 11:17
4 discussed and explained by Dr. Guengerich, to slow 11:17
5 and reduce the formation of lipofuscin in the eye 11:17
6 and by reducing A2E and ATR dimer formation. 11:17
7 Q. And are you relying on Dr. Guengerich for 11:17
8 what would be expected from C20 deuteration of 11:17
9 vitamin A, or do you have your own independent 11:17
10 expertise to evaluate that? 11:17
11 A. Give me just a minute. 11:17
12 So I've read -- I've read the literature 11:18
13 that I've cited. I read it as a clinician, not as 11:18
14 a chemist. And the literature that I have read 11:18
15 indicates that formation of A2E and ATR dimer is 11:18
16 involved in lipofuscin formation which, as a 11:18
17 clinician, I know is part of the path of 11:18
18 physiology of these diseases. 11:18
19 So therefore, as a clinician and having 11:18
20 some knowledge of the relevant literature at the 11:18
21 time, I would -- I would be wanting to find a way 11:18
22 to reduce formation of lipofuscin precursors. 11:18
23 And according to Dr. Guengerich, 11:19
24 deuteration at C20 of vitamin A would be a 11:19
25 reasonable approach to -- to have that 11:19

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1 pharmacological effect. 11:19

2 Q. And do you have your own independent 11:19

3 expertise to evaluate whether deuteration at C20 of 11:19

4 vitamin A would be a reasonable approach to have 11:19

5 that pharmacological effect, or is that wholly 11:19

6 reliant on Dr. Guengerich? 11:19

7 MR. MILLS: Objection to form. Asked and 11:19

8 answered. 11:19

9 THE WITNESS: So I'm relying on 11:19

10 Dr. Guengerich for the chemical aspects of that -- 11:19

11 and specifics of that C20 deuteration. But as I 11:19

12 cited in my report, I and a POSA in 2007 would 11:19

13 have been aware of deuteration as an approach. 11:19

14 And as a clinician in 2007, I was aware of 11:20

15 lipofuscin formation and macular degeneration and 11:20

16 associated dystrophies. 11:20

17 And as a POSA in 2007, I would have been 11:20

18 aware of the various papers discussing the 11:20

19 metabolic pathways, including the harmful 11:20

20 pathways, which we can differ on whether or not 11:20

21 it's metabolic, that result in formation of 11:20

22 insoluble harmful species such as A2E and ATR 11:20

23 dimer. 11:20

24 So I do have -- when you say my 11:20

25 independent expertise, again, I'm putting myself 11:20

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1	as a POSA at the time of the priority date, having	11:20
2	researched the literature in those areas, and	11:20
3	integrating that as a clinical -- as a clinician	11:20
4	POSA, these are my opinions, as stated in my	11:20
5	report.	11:21
6	BY MR. FELDSTEIN:	11:21
7	Q. Do you have an understanding of what a	11:21
8	person of ordinary skill in the art would have	11:21
9	known in the 2007-2008 time frame as to when	11:21
10	deuteration will or will not slow down a chemical	11:21
11	reaction?	11:21
12	MR. MILLS: Objection. Form. Asked and	11:21
13	answered.	11:21
14	THE WITNESS: Can I just see that?	11:21
15	All right. When we've discussed person of	11:21
16	ordinary skill in the art, we've explained that --	11:21
17	and I believe the other -- the patent holder has	11:21
18	made a similar assertion -- that POSA would	11:21
19	include a team of people who have requisite	11:21
20	knowledge and expertise.	11:21
21	If there is a Ph.D. chemist with	11:21
22	experience in deuteration who is also treating	11:22
23	retinal patients as an M.D., I'm not aware that	11:22
24	that person exists.	11:22
25	And so my contribution to the analysis is	11:22

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1	as a clinician POSA. Dr. Guengerich's	11:22
2	contribution to the analysis is as a chemist POSA.	11:22
3	So I'm not sure if I got abroad from what	11:22
4	your question was. Oh, what a person would have	11:22
5	known in the time frame...	11:22
6	So I think Dr. Guengerich would have had a	11:22
7	more detailed knowledge as to when deuteration	11:22
8	will or will not slow down a chemical reaction.	11:22
9	As a clinician POSA, I have no	11:22
10	independent -- I have never worked independently	11:22
11	with deuterated compounds. But the references	11:22
12	that I disclose, which we just went through, which	11:22
13	are available, were available to the POSA, do have	11:22
14	some material that's responsive to that, that at	11:22
15	least give us a concept of, you know, when	11:23
16	deuteration will or will not slow down a reaction.	11:23
17	And there's some information on Blake.	11:23
18	I'm not going to go through it now, but it talks	11:23
19	about the biggest effects being seen when the	11:23
20	carbon-hydrogen bond is at the active site of the	11:23
21	reaction, but that some deuteration at more	11:23
22	distant sites can have smaller effects as well.	11:23
23	So again, I would defer to Dr. Guengerich	11:23
24	on the details, but I, as a clinician POSA working	11:23
25	on this type of project in 2007, would have had	11:23

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1	that background knowledge.	11:23
2	BY MR. FELDSTEIN:	11:23
3	Q. And sitting here today, Dr. Calman, what	11:23
4	is your understanding, if any, of what a person of	11:23
5	ordinary skill would have known in the 2007-2008	11:23
6	time frame as to when deuteration will or will not	11:23
7	slow down a chemical reaction?	11:23
8	MR. MILLS: Objection to form. Asked and	11:24
9	answered.	11:24
10	THE WITNESS: I think I covered that, but	11:24
11	I'll try to do it more succinctly.	11:24
12	A POSA would have been a member of a team.	11:24
13	There would have been typically, as we're	11:24
14	discussing here, a chemist POSA and a clinician	11:24
15	POSA.	11:24
16	The clinician POSA would have been aware	11:24
17	of the prior art, including, for example, the	11:24
18	Blake reference, Exhibit 1047, which discuss the	11:24
19	larger effect of deuteration at an active reaction	11:24
20	site compare to a lesser effect at a more distant	11:24
21	site.	11:24
22	And a POSA chemist, such as	11:24
23	Dr. Guengerich, would have had a much more	11:24
24	detailed nuts and bolts knowledge of when a	11:24
25	deuteration would or would not have an effect on a	11:24

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1	particular reaction.	11:24
2	With that, can we maybe take a break?	11:24
3	MR. FELDSTEIN: Sure. Off the record.	11:24
4	(Lunch break taken.)	12:37
5	BY MR. FELDSTEIN:	12:37
6	Q. Can you turn, Doctor, in your declaration,	12:37
7	Exhibit 1004, to paragraph 143.	12:37
8	A. Again, we are in the '045 version?	12:37
9	Q. Yes. Unless I say otherwise, we're going	12:37
10	to stick to the '045 patent, the 00313 IPR.	12:38
11	In paragraph 145, you're talking about the	12:38
12	concept of partially replacing the non-deuterated	12:38
13	vitamin A?	12:38
14	Do you see that?	12:38
15	A. I do.	12:38
16	Q. The concept of partially replacing vitamin	12:38
17	A in the ocular tissue, that's not something	12:38
18	that's taught in any of the references that you	12:38
19	rely on; is that correct?	12:38
20	MR. MILLS: Objection. Form.	12:38
21	THE WITNESS: Pharmacologically. Let me	12:38
22	look at the question here. I guess -- you know,	12:38
23	again, this may be semantics, but Ortho Pharma	12:38
24	teaches administering vitamin A for treatment of	12:38
25	macular degeneration and other age-related eye	12:38

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1	disease.	12:38
2	So I guess it's semantics whether giving	12:38
3	that is partially replacing vitamin A.	12:39
4	BY MR. FELDSTEIN:	12:39
5	Q. Why don't we turn to Ortho, then, if	12:39
6	that's where you want to go. Ortho is about	12:39
7	supplementing, not replacing; isn't that correct?	12:39
8	A. Here again, I think that's what I meant by	12:39
9	semantics, is supplementing the same as replacing	12:39
10	or different from replacing.	12:39
11	Q. Ortho is Exhibit 1008; right?	12:39
12	Can you explain what you mean that it's	12:39
13	semantics on whether Ortho is teaching	12:39
14	supplementing versus replacing?	12:39
15	A. Well, I think from a logical standpoint,	12:39
16	some of the molecules that are ending up in the	12:39
17	retina that are derived from the compositions	12:39
18	disclosed in Ortho -- Ortho Pharma will take the	12:39
19	place of molecules that otherwise would have been	12:40
20	absorbed from dietary sources of carotinoids. So	12:40
21	is it supplementation, or is it replacement?	12:40
22	Again, it's a semantic -- the terms have some	12:40
23	overlap, and I think it's a semantic distinction.	12:40
24	Q. Is there something specific that you would	12:40
25	point to in Ortho that addresses whether it's	12:40

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1	supplementing or replacing?	12:40
2	A. I mean, I would have to go through the	12:40
3	whole thing and see if there's language that's	12:40
4	pertinent to that.	12:40
5	Q. That's fine. Take your time.	12:41
6	A. So the Ortho Pharma patent uses a variety	12:43
7	of terms, including (as read):	12:43
8	"Dietary treatment, dietetic treatment, supply, and	12:43
9	supplement. And in particular, dietary treatment of	12:43
10	eye diseases, in particular, age-related eye	12:43
11	diseases."	12:43
12	Q. I'm sorry. Where are you reading?	12:43
13	A. Claim 15 is for the latter thing. I don't	12:44
14	see the word "replace."	12:44
15	Q. If you turn to paragraph 9, for example,	12:44
16	the context is correcting an inadequate supply of	12:44
17	vitamins and nutrients; correct?	12:44
18	A. I'm sorry. You are on claim --	12:44
19	Q. I'm sorry. Paragraph 3.	12:44
20	A. Paragraph 3 or claim 3?	12:44
21	Q. Paragraph 3, sir.	12:44
22	A. As I said, that's one of several. (As	12:44
23	read):	12:44
24	"Supply, supplement, dietary treatment, dietetic	12:44
25	treatment, including dietary treatment of eye	12:44

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1 diseases, in particular, age-related eye diseases." 12:44

2 Q. In paragraph 3, it's talking about the 12:44

3 context of there being an inadequate supply, and 12:44

4 that's what they were trying to overcome in this 12:44

5 patent; correct? 12:45

6 MR. MILLS: Objection to form. 12:45

7 THE WITNESS: It actually says (as read): 12:45

8 "An incorrect diet or an inadequate supply of the 12:45

9 necessary vitamins and nutrients." 12:45

10 BY MR. FELDSTEIN: 12:45

11 Q. And then it refers to the state of the art 12:45

12 being in the context of preventing deficiencies in 12:45

13 the supply; correct? 12:45

14 A. It says (as read): 12:45

15 "In the state of the art, supportive care, especially 12:45

16 for elderly patients, is known to prevent 12:45

17 deficiencies in the supply of vitamins and nutrients 12:45

18 to the eye." 12:45

19 Q. So the context here is, we need to 12:45

20 supplement the supply of vitamins, not replace the 12:45

21 supply of vitamins; correct? 12:45

22 MR. MILLS: Objection to form. 12:45

23 THE WITNESS: Well, that's one of the 12:45

24 things that it says. But it also says (as read): 12:45

25 "It is well known that age-related eye diseases such 12:45

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1 as age-related macular degeneration or senile 12:45
2 cataract have greatly increased and will continue to 12:45
3 increase due to the rising average age of the 12:46
4 population." 12:46
5 Then in claim 15, it talks about dietary 12:46
6 treatment of eye diseases, in particular, 12:46
7 age-related eye diseases. 12:46
8 BY MR. FELDSTEIN: 12:46
9 Q. In paragraph 2 that you are reading, there 12:46
10 is no indication of replacing, either partially or 12:46
11 otherwise; correct? 12:46
12 MR. MILLS: Objection to form. 12:46
13 THE WITNESS: Again, I think we're hung up 12:46
14 on the semantics of "replace." 12:46
15 My reading is, whether you interpret this 12:46
16 as a supply, a supplementation, a dietary 12:46
17 treatment, or a dietetic treatment, there are 12:46
18 molecules of these -- of these ingredients that 12:46
19 are going to, some of them, end up in ocular 12:46
20 tissue, some of which may displace other molecules 12:46
21 of the same or similar substances that may have 12:46
22 been absorbed from dietary sources. 12:46
23 BY MR. FELDSTEIN: 12:46
24 Q. Ortho itself is not talking about and 12:47
25 doesn't refer to displacing, as you just stated; 12:47

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1 correct? 12:47

2 MR. MILLS: Objection to form. 12:47

3 THE WITNESS: I don't -- I didn't see the 12:47

4 word "displace" -- I don't recall seeing the word 12:47

5 "displace" in the Ortho patent. 12:47

6 BY MR. FELDSTEIN: 12:47

7 Q. Okay. And while we're talking about 12:47

8 Ortho, Ortho distinguishes vitamin A from beta 12:47

9 carotene; correct? 12:47

10 MR. MILLS: Objection to form. 12:47

11 THE WITNESS: So to put that in context, 12:47

12 as you know, there are different authors who use 12:47

13 the term "vitamin A" differently, and I cited one 12:47

14 of them that includes beta carotene within that 12:47

15 heading of vitamin A. 12:47

16 BY MR. FELDSTEIN: 12:47

17 Q. Sure. Why don't we just talk about Ortho 12:47

18 for a moment. Ortho distinguishes vitamin A from 12:47

19 beta carotene; correct? 12:47

20 MR. MILLS: Objection to form. 12:47

21 THE WITNESS: I'm looking. I'm seeing 12:47

22 vitamin A listed in paragraph 8. 12:47

23 BY MR. FELDSTEIN: 12:47

24 Q. Separately from beta carotene in 12:47

25 paragraph 8; correct? 12:47

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1 A. Yeah, they do list it separately. 12:47

2 Q. And Ortho nowhere identifies any function 12:48

3 of vitamin A other than with respect to 12:48

4 | nutritional deficiencies; correct? 12:48

5 MR. MILLS: Objection to form. 12:48

6 THE WITNESS: Well, once again, I think 12:48

7 | that would be included within the language of 12:48

8 | claim 15 where it's an agent for the dietary | 12:48

9 treatment of eye diseases, in particular, 12:48

10	age-related eye diseases such as age-related	12:48
----	--	-------

11	macular degeneration or senile cataract.	12:48
----	--	-------

12 BY MR. FELDSTEIN: 12:48

13 Q. Claim 15 doesn't refer to the use of 12:48

14	vitamin A; correct?	12:48
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15	MR. MILLS: Objection to form.	12:48
----	-------------------------------	-------

16	THE WITNESS: Well, I would disagree with	12:48
----	--	-------

17 that because a carotinoid and vitamin A are -- 12:48

18 are -- again, different people have different 12:48

19 terms, but for the most part, those are 12:48

20 overlapping terms. 12:48

21 BY MR. FELDSTEIN: 12:48

22	Q. In the context of Ortho, carotinoids	12:48
----	---	-------

23	include beta carotene, lutein, zeaxanthin and	12:49
----	---	-------

24 lycopene, but not vitamin A; correct? 12:49

25	MR. MILLS: Objection to form.	12:49
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1 THE WITNESS: I don't see that. I see 12:49
2 that they list it separately, but that doesn't 12:49
3 necessarily mean that vitamin A is not included as 12:49
4 a carotinoid. I think most authors would include 12:49
5 vitamin A as a carotinoid. 12:49
6 BY MR. FELDSTEIN: 12:49
7 Q. Okay. Why don't we just stick with what 12:49
8 Ortho actually teaches. And where Ortho was 12:49
9 referring to carotinoids, they define a group that 12:49
10 is beta carotene, luetin, zeaxanthin, and 12:49
11 lycopene; correct? 12:49
12 MR. MILLS: Objection to form. 12:49
13 THE WITNESS: So I think you're referring 12:49
14 to paragraph 41, but maybe you can point me to 12:49
15 what you're using as the basis for that statement. 12:50
16 BY MR. FELDSTEIN: 12:50
17 Q. Okay. Just as whole, you read the whole 12:50
18 paragraph, the whole thing; correct? 12:50
19 A. Well, I would say that, again, this is 12:50
20 semantics. This is almost more of a discussion 12:50
21 for a philosophy class than a science class. 12:50
22 But the fact that carotinoids -- it says, 12:50
23 "Carotinoids selected from the group comprising 12:50
24 lutein, zeaxanthin, and lycopene." And elsewhere 12:50
25 in the paragraph, it says, "Vitamin A." 12:50

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1 That, to me, does not logically preclude 12:50
2 vitamin A from being a carotinoid. It simply says 12:50
3 that in addition to vitamin A -- or in addition to 12:50
4 vitamin A being one of the vitamins selected from 12:50
5 a group containing vitamin A and a number of other 12:50
6 vitamins and other ingredients, there is a 12:50
7 separate delineation that, one, there will be a 12:50
8 capsule containing Omega-3 fatty acids, l-cystine, 12:50
9 and carotinoids selected from the group comprising 12:51
10 lutein, zeaxanthin, and lycopene. 12:51
11 That doesn't mean that vitamin A can't be 12:51
12 a carotinoid. And a POSA would know that 12:51
13 vitamin A is a carotinoid. "Vitamin A" is a 12:51
14 collective term including carotinoids. 12:51
15 Q. Are you done, Doctor? 12:51
16 A. That's my answer. 12:51
17 Q. Ortho specifically identifies certain 12:51
18 carotinoids; correct? 12:51
19 MR. MILLS: Objection. Form. 12:51
20 THE WITNESS: Well, again, I think you're 12:52
21 trying to twist it be a little bit. Ortho uses 12:52
22 the term "carotinoids," and in this paragraph and 12:52
23 likely in others, it provides a subset of 12:52
24 carotinoids that delineate, which does not 12:52
25 necessarily serve as a restrictive definition of 12:52

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1	the term "carotinoids."	12:52
2	BY MR. FELDSTEIN:	12:52
3	Q. And what subset of carotinoids are	12:52
4	affirmatively identified as carotinoids in Ortho?	12:52
5	MR. MILLS: Objection. Form.	12:52
6	THE WITNESS: Well, the ones that are	12:52
7	included within the subset that are listed for the	12:52
8	purposes of this embodiment, which does not	12:52
9	necessarily exclude other carotinoids from being	12:52
10	carotinoids, especially given the plain and	12:52
11	ordinary meaning of the terms and the knowledge of	12:52
12	a POSA in 2007, comprise -- which to my	12:52
13	understanding means that that does not mean it's	12:52
14	an exclusive list -- comprise lutein, zeaxanthin,	12:52
15	and lycopene.	12:53
16	And that's looking at paragraph 41. There	12:53
17	may be other variations elsewhere. I see a	12:53
18	similar list in 42.	12:53
19	BY MR. FELDSTEIN:	12:53
20	Q. You agree there is nowhere that vitamin A	12:53
21	is listed among the group of carotinoids; correct?	12:53
22	MR. MILLS: Objection. Form.	12:53
23	THE WITNESS: Subject to all of the	12:53
24	caveats that I expressed in my previous answer, I	12:53
25	think that's true.	12:53

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1	BY MR. FELDSTEIN:	12:53
2	Q. And leaving aside whatever Ortho teaches	12:53
3	for carotinoids, it doesn't provide any other or	12:53
4	additional function for vitamin A; correct?	12:53
5	MR. MILLS: Objection to form.	12:54
6	THE WITNESS: It's a long document, so	12:54
7	give me a moment.	12:54
8	BY MR. FELDSTEIN:	12:54
9	Q. Take your time, Doctor.	12:54
10	A. I don't see a specific function listed for	12:55
11	vitamin A in this document.	12:55
12	Q. In what type of dosage form does Ortho	12:55
13	teach in administering vitamin A in combination	12:55
14	with other supplements?	12:55
15	MR. MILLS: Objection to form.	12:55
16	THE WITNESS: A liquid dosage form.	12:55
17	BY MR. FELDSTEIN:	12:56
18	Q. Did you see anywhere where Ortho teaches	12:56
19	administering vitamin A in combination with other	12:56
20	supplements where they're all contained within a	12:56
21	single solid dosage form?	12:56
22	A. Not explicitly, although I think claim 17	12:56
23	is, arguably, ambiguous.	12:56
24	Q. It's correct Ortho doesn't disclose using	12:56
25	deuterated vitamin A compounds; correct?	12:56

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1	A. That is true.	12:57
2	Q. And it's also true that Ortho is not	12:57
3	directed to the treatment of Stargardt's disease;	12:57
4	correct?	12:57
5	MR. MILLS: Objection.	12:57
6	THE WITNESS: Well, it is directed -- so	12:57
7	in claim 15, the invention is directed toward an	12:57
8	agent for the dietary treatment of eye diseases,	12:57
9	in particular, age-related eye diseases such as	12:57
10	age-related macular degeneration or senile	12:57
11	cataracts. It does not mention Stargardt's.	12:58
12	Stargardt's is generally not a disease of	12:58
13	the elderly; however, a person of ordinary skill	12:58
14	in the art would know that other macular	12:58
15	degenerations exist which are related to	12:58
16	age-related macular degeneration in some ways.	12:58
17	BY MR. FELDSTEIN:	12:58
18	Q. Can we turned back to where we jumped off	12:58
19	from, paragraph 145 of your declaration,	12:58
20	Exhibit 1004. We were looking at the statement	12:58
21	about partially replacing or partially replace.	12:58
22	Were there any other references besides	12:58
23	Ortho that, in your view, taught the desirable of	12:58
24	partially replacing non-deuterated vitamin A in	12:58
25	the ocular tissue?	12:58

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1	MR. MILLS: Objection. Form.	12:58
2	THE WITNESS: So I'm not -- nothing is	12:58
3	springing to mind, but if it's in my report, I	12:58
4	stand by it.	12:59
5	BY MR. FELDSTEIN:	12:59
6	Q. In this opinion in the first sentence of	12:59
7	paragraph 145, are you again relying on	12:59
8	Dr. Guengerich for what the expected chemical	12:59
9	effects of C20 retinoid deuteration would be?	12:59
10	A. I'm relying on Dr. Guengerich for some of	12:59
11	the molecular details, as I have discussed in	12:59
12	previous answers, and I'm also relying on the	12:59
13	prior art that I cited which would have been	12:59
14	available and understandable by a clinical POSA in	12:59
15	2007 indicating the desirability of reducing A2E	12:59
16	and ATR dimer precursors to lipofuscin.	12:59
17	Q. In the next sentence of paragraph 145 of	12:59
18	your declaration, Exhibit 1004, you talk about	13:00
19	C20-deuterated vitamin A could potentiate the	13:00
20	effect of drugs such as fenretinide and	13:00
21	isotretinoin; correct?	13:00
22	A. It does say that, the fenretinide and the	13:00
23	isotretinoin.	13:00
24	Q. It comes out identical on the transcript	13:00
25	even if I mispronounce it, so it's great.	13:00

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1	There are no references that you cite that	13:00
2	teach the idea of using deuterated vitamin A to	13:00
3	potentiate the effect of these drugs; correct?	13:00
4	MR. MILLS: Objection to form.	13:00
5	THE WITNESS: I would disagree. Let me --	13:00
6	let's look at the Widder reference.	13:00
7	BY MR. FELDSTEIN:	13:00
8	Q. I'm sorry, which reference?	13:00
9	A. W-i-d-d-e-r.	13:00
10	Q. So a POSA reading Widder would have	13:01
11	inferred -- let me just make sure I'm responsive	13:01
12	to your question.	13:01
13	So Widder, W-i-d-d-e-r, teaches the	13:01
14	reduction of -- more slowing of the visual cycle	13:01
15	uses drugs such as fenretinide. It also mentions	13:01
16	side effects including delayed dark adaptation,	13:01
17	night blindness.	13:01
18	And I think you may have even asked me a	13:01
19	question about this material earlier this morning,	13:01
20	and I wasn't recalling Widder.	13:01
21	But in any case, a POSA would have	13:01
22	understood, even though Widder does not explicitly	13:02
23	mention deuterated vitamin A, that a drug that	13:02
24	would reduce the diversion of all-trans-retinal to	13:02
25	undesirable and harmful lipofuscin precursors	13:02

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1	might enable use of drugs similar to fenretinide	13:02
2	or fenretinide itself at lower doses with lower	13:02
3	risks of side effects.	13:02
4	Q. With respect to vitamin A levels, Widder,	13:02
5	Exhibit 1009, is premised on reducing circulating	13:02
6	vitamin A levels; correct?	13:02
7	MR. MILLS: Objection to form.	13:02
8	THE WITNESS: Not entirely. And let me	13:02
9	find the relevant portion of my declaration.	13:02
10	So if you turn to paragraph 145 of my	13:03
11	declaration, it addresses the mechanism of action	13:03
12	of fenretinide, which they also refer to as HPR.	13:03
13	And what they find is that -- and this also may	13:03
14	have been responsive to some of your questions	13:03
15	earlier today about serum levels of vitamin A	13:03
16	where I was blanking on this.	13:03
17	But, in any case, Widder addresses the	13:03
18	fact that HPR or fenretinide has been shown to	13:03
19	cause marked inhibition of LRAT activity, which is	13:03
20	lecithin retinol acyltransferase. And that it	13:03
21	inhibits LRAT activity in membranes prepared from	13:04
22	liver and small intestine, but it also -- but they	13:04
23	demonstrate for the first time that it also	13:04
24	inhibits LRAT activity in the RPE of the eye.	13:04
25	And therefore, they attribute effects to	13:04

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1	HPR or fenretinide both in terms of decreasing	13:04
2	serum retinol, r-e-t-i-n-o-l, and also an	13:04
3	intracellular enzyme-specific effect in RPE cells,	13:04
4	suggesting -- and they also suggest that the	13:04
5	effects of fenretinide may be most pronounced in	13:04
6	the eye.	13:04
7	So yes, to some degree, they do attribute	13:04
8	the effects of HPR or fenretinide to reducing	13:04
9	serum vitamin A levels, but they also reveal a --	13:05
10	or disclose a direct effect in the eye.	13:05
11	Q. So you're using the example of HPR as the	13:05
12	basis for what you say in paragraph 145, that a	13:05
13	POSA would have understood that C22-grade vitamin	13:05
14	A could potentiate the effects of drugs such as	13:05
15	fenretinide and isotretinoin?	13:05
16	A. Well, I would say that's the one that --	13:05
17	the best studied. There is also literature on	13:05
18	isotretinoin, which is also referenced in Widder,	13:06
19	and Widder also talks about phospholipids, which	13:06
20	can inhibit apoptosis.	13:06
21	And again, you know, a clinical POSA	13:06
22	understands that sometimes when you use drugs in	13:06
23	combination to target multiple aspects of a	13:06
24	pathway, that you can sometimes reduce the doses	13:06
25	and reduce the side effects.	13:06

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1	Q. When you say "potentiate the effect of	13:06
2	drugs," you're referring to just reducing the	13:07
3	dosages thereof?	13:07
4	A. Well, not necessarily. "Potentiate"	13:07
5	usually means to make more effective or --	13:07
6	Q. Is that --	13:07
7	A. Wait a minute.	13:07
8	-- or to make more potent, and potency and	13:07
9	effectiveness are different pharmacologically.	13:07
10	Potency is typically the amount of effect per unit	13:07
11	dose.	13:07
12	And so typically, what you're seeing when	13:07
13	you have this sort of pharmacological scenario is	13:07
14	you are either creating a desirable increased	13:07
15	effect, or you're allowing for lower doses, which	13:07
16	can reduce the risk of side effects.	13:07
17	Q. Are you done, Doctor?	13:07
18	A. Yeah.	13:07
19	Q. You wrote this sentence in the middle of	13:07
20	paragraph 145 about "potentiate"; correct?	13:07
21	A. Paragraph 145?	13:07
22	Q. Yes.	13:07
23	A. Let's see.	13:08
24	Q. In paragraph 145, ten lines down, you	13:08
25	refer to "potentiate"; correct?	13:08

1	A. Okay. I see the sentence now.	13:08
2	Q. My question for you is, what did you mean	13:08
3	by "potentiate" when you wrote it in paragraph 145	13:08
4	of Exhibit 1004?	13:08
5	A. That's a different question, but I'll be	13:08
6	happy to answer it. And I think I kind of already	13:08
7	did. And I think it, to some degree, even speaks	13:08
8	for itself.	13:08
9	To put this in context, again, Widder	13:08
10	discloses that -- and other references as well --	13:08
11	that these drugs can have side effects, including	13:08
12	night blindness, delayed visual adaptation.	13:08
13	And the concept is that by targeting	13:08
14	another aspect of this pathway, specifically by	13:08
15	using C20-deuterated vitamin A to reduce the	13:09
16	formation of undesirable lipofuscin precursors	13:09
17	without slowing the visual cycle, it may be	13:09
18	possible to use those visual cycle-slowng drugs	13:09
19	at lower doses where the therapeutic ratio of	13:09
20	beneficial effects to harmful side effects, such	13:09
21	as night blindness, would be more favorable.	13:09
22	And in answer to your other question, yes,	13:09
23	I did write this sentence.	13:09
24	Q. When you use the word "potentiate" here in	13:09
25	paragraph 145, you're saying that a POSA would	13:09

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1	have understood that C20-deuterated vitamin A would	13:09
2	make these other drugs more effective? Is that	13:09
3	what this says?	13:09
4	A. I think this is the third time you're	13:09
5	asking this, and I've already answered it, but	13:09
6	I'll do it again.	13:09
7	Q. But before, Doctor --	13:09
8	MR. MILLS: Counsel, please don't	13:09
9	interrupt the witness.	13:09
10	THE WITNESS: So I guess I'll just recite	13:10
11	what I said before.	13:10
12	"Potentiate" can mean make more effective	13:10
13	or make more potent, and potent in pharmacology	13:10
14	means efficacy divided by dosage.	13:10
15	And so the clinical meaning here is that	13:10
16	by inhibiting this pathway with C20-deuterated	13:10
17	vitamin A to reduce the formation of harmful	13:10
18	lipofuscin precursors without slowing the visual	13:10
19	cycle, it may be possible to use these drugs such	13:10
20	as fenretinide and other drugs that can slow the	13:10
21	visual cycle, thus continuing their beneficial	13:10
22	effects while minimizing their side effects,	13:10
23	including potentially using them at lower doses	13:10
24	than you would if they were used as a sole	13:11
25	therapeutic agent.	13:11

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1	BY MR. FELDSTEIN:	13:11
2	Q. So your testimony just now was that using	13:11
3	them in combination, quote, it may be possible,	13:11
4	close quote, to use lower doses. What's the	13:11
5	difference between "may be possible," as you just	13:11
6	testified, and what you state in paragraph 145	13:11
7	that a POSA would have understood?	13:11
8	MR. MILLS: Objection. Form.	13:11
9	THE WITNESS: Well, I would have	13:11
10	understood that it could. I think the operative	13:11
11	word here is "could" potentiate. I'm not saying	13:11
12	it definitely would. I think you would have to do	13:11
13	the experiment to know for sure.	13:11
14	But a POSA would have understood that this	13:11
15	is not a unique scenario in medicine. This is --	13:11
16	this is an avenue for potential therapy with	13:11
17	multiple agents, and that it is something that	13:11
18	would be worth investigating and potentially	13:11
19	testing.	13:12
20	BY MR. FELDSTEIN	13:12
21	Q. And in terms of the effects of	13:12
22	C20-deuterated vitamin A on slowing the formation	13:12
23	of lipofuscin, the chemistry of that slowing is	13:12
24	again based on the testimony of Dr. Guengerich;	13:12
25	correct?	13:12

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1	MR. MILLS: Objection. Asked and	13:12
2	answered.	13:12
3	THE WITNESS: Right. I think to the	13:12
4	extent we're talking about the mechanism or the	13:12
5	magnitude of that effect, I am relying on	13:12
6	Dr. Guengerich for that chemistry.	13:12
7	BY MR. FELDSTEIN:	13:12
8	Q. Turn to paragraph 200 of your declaration,	13:12
9	1004. You refer in paragraph 200 to Mata	13:12
10	Figure 5; is that correct?	13:13
11	A. I see that reference. I'm looking for	13:13
12	that Exhibit 1010. If you're going to ask me	13:13
13	questions about Mata, I'm going to want to read	13:13
14	it.	13:13
15	Q. Sure. The first question just is, do you	13:13
16	have your own independent expertise with respect	13:13
17	to Mata Figure 5, or are you relying on	13:13
18	Dr. Guengerich's analysis that you've previously	13:13
19	discussed?	13:13
20	A. So I have some knowledge about the -- as a	13:13
21	clinician, treating these patients. And having	13:13
22	some background in biochemistry, I have a	13:13
23	knowledge of the visual cycle in general. And I	13:13
24	have a knowledge of formation of various dimer	13:13
25	products of ATR in the formation of lipofuscin. I	13:13

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1 have knowledge of lipofuscin in macular disease. 13:13

2 In terms of the specific rearrangements 13:14

3 that are depicted in the steps, the chemical 13:14

4 steps, I defer to Dr. Guengerich on that. 13:14

5 Q. Do you have an understanding, separate 13:14

6 from anything that Dr. Guengerich had said, as to 13:14

7 whether the hypothetical biosynthetic pathway 13:14

8 depicted in Figure 5 of Mata was -- there was a 13:14

9 consensus -- let me start again. 13:14

10 Do you have an understanding, separate 13:14

11 from anything Dr. Guengerich has said, that as of 13:14

12 2007-2008, there was consensus that the 13:14

13 hypothetical biosynthetic pathway depicted in Mata 13:14

14 Figure 5 was correct? 13:14

15 MR. MILLS: Objection. Form. 13:14

16 THE WITNESS: I'll tell you what I'm aware 13:14

17 of. What I'm aware of is that Fishkin published 13:14

18 two papers and noted an additional pathway 13:14

19 creating ATR dimer, which is identified in 13:15

20 Figure 10 of Fishkin 2005, Exhibit 1011. 13:15

21 As to the details of any -- and I also am 13:15

22 aware that they depict the molecules in different 13:15

23 ways, which is, you know, not entirely edifying. 13:15

24 But in terms of the details of any disagreement, I 13:15

25 would defer to Dr. Guengerich. 13:15

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1	BY MR. FELDSTEIN:	13:15
2	Q. Okay. Fair enough.	13:15
3	Can you turn to Exhibit 1040, the Berson	13:16
4	reference.	13:16
5	A. Yes.	13:16
6	Q. Exhibit 1040, Berson, is about retinitis	13:16
7	pigmentosa; correct?	13:16
8	A. Yeah. I should read this. Give me a	13:16
9	minute.	13:16
10	Okay.	13:23
11	Q. So the question was --	13:23
12	A. Sorry.	13:23
13	Q. The question was, Exhibit 1040, Berson, is	13:23
14	about retinitis pigmentosa; is that correct?	13:23
15	A. Yes.	13:23
16	Q. If we turn to page 771, last page of the	13:23
17	text, last paragraph at the bottom begins, "The	13:23
18	mechanism."	13:23
19	Do you see that?	13:23
20	A. I see that.	13:23
21	Q. It indicates (as read):	13:23
22	"The mechanism by which vitamin A affects the course	13:23
23	of retinal degradation in retinitis pigmentosa	13:23
24	remains to be clarified."	13:23
25	Do you see that?	13:23

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1 A. You said "degradation," but I think you 13:23
2 meant to say "degeneration." 13:24
3 Q. Correct. Thank you so much. 13:24
4 Other than my mispronounce -- misreading a 13:24
5 word, is it correct that as of 2007-2008, the 13:24
6 mechanism by which vitamin A supplementation 13:24
7 affects the course of retinal degeneration in 13:24
8 retinitis pigmentosa remained to be clarified? 13:24
9 MR. MILLS: Objection to form. 13:24
10 THE WITNESS: I think that's probably a 13:24
11 fair statement. 13:24
12 BY MR. FELDSTEIN: 13:24
13 Q. And Berson, Exhibit 1040, doesn't identify 13:24
14 the mechanism for vitamin A to treat any disease 13:24
15 other than retinitis pigmentosa; correct? 13:24
16 A. I didn't see anything regarding other 13:24
17 diseases in that publication. 13:24
18 Q. If we go to the very last sentence of the 13:24
19 article, it's a long sentence. It begins, "Based 13:24
20 on these findings." 13:25
21 Do you see that? 13:25
22 A. I do. 13:25
23 Q. And then it gives a recommendation to give 13:25
24 adult patients with common forms of retinitis 13:25
25 pigmentosa a vitamin A supplement; correct? 13:25

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1 A. I see that. 13:25

2 Q. Berson doesn't recommend giving vitamin A 13:25

3 supplements to patients with diseases other than 13:25

4 retinitis pigmentosa; correct? 13:25

5 MR. MILLS: Objection. Form. 13:25

6 THE WITNESS: Well, the publication is 13:25

7 silent on application of these results outside of 13:25

8 patients with retinitis pigmentosa. 13:25

9 BY MR. FELDSTEIN: 13:25

10 Q. Is retinitis pigmentosa something that you 13:25

11 currently treat? 13:25

12 A. Well, we don't really have good treatment, 13:25

13 and I think it would be fair to say that my -- my 13:25

14 evaluation and management of patients with 13:25

15 retinitis pigmentosa for the most part is similar 13:25

16 to my management of patients with retinol 13:25

17 dystrophies. 13:25

18 I should say there is one -- there is one 13:25

19 subgroup of patients who have been shown to 13:26

20 benefit from a gene therapy that is approved by 13:26

21 the FDA. It's a small subset, and the effect is 13:26

22 not great, and it's extremely expensive. 13:26

23 But other treatments are also in 13:26

24 development. So when I encounter these patients, 13:26

25 I typically diagnose them or at least give them a 13:26

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1	presumptive diagnosis and refer them for genetic	13:26
2	testing and management to Dr. Duncan at UCSF	13:26
3	because she is the person in our area with the	13:26
4	most experience with inherited retinal disease,	13:26
5	including retinitis pigmentosa.	13:26
6	Q. So you see -- among the patients you see,	13:26
7	you do see patients that have retinal pigmentosa;	13:26
8	is that correct?	13:26
9	A. I think you meant to say retinitis	13:26
10	pigmentosa.	13:26
11	And I do see patients with retinitis	13:26
12	pigmentosa on occasion, yes.	13:26
13	Q. And do you provide -- prescribe for them	13:26
14	to take high doses of vitamin A supplements?	13:26
15	A. So this recommendation was current as of	13:27
16	2007, but subsequent research has failed to	13:27
17	confirm it. And so current treatment	13:27
18	recommendations do not include this.	13:27
19	Q. So current standard of care for retinitis	13:27
20	pigmentosa patients is not prescribing high doses	13:27
21	of vitamin A; is that correct?	13:27
22	A. That is my understanding. And if you --	13:27
23	but that's not the subtotal -- sum total of the	13:27
24	standard of care for retinitis pigmentosa, which	13:27
25	is a very broad group of diseases.	13:27

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1	Q. Around 2007 and 2008, did you personally	13:27
2	prescribe high doses of vitamin A to patients with	13:27
3	retinitis pigmentosa?	13:27
4	A. So these are not prescription drugs.	13:27
5	These are nutritional supplements. Typically, in	13:27
6	2007, I was -- I would make a presumptive	13:27
7	diagnosis and refer them to UCSF for additional	13:27
8	testing, including genetic testing, as well as	13:27
9	electroretinography and other electrophysiologic	13:28
10	testing.	13:28
11	And, you know, we would probably discuss	13:28
12	nutrition at that point, but generally, I would	13:28
13	defer until they were definitively diagnosed at	13:28
14	the university.	13:28
15	I'm trying to recall if there was ever a	13:28
16	patient who refused referral. I suppose if they	13:28
17	had, I probably would have made the recommendation	13:28
18	for nutritional supplements in accordance with	13:28
19	this publication at that time.	13:28
20	Q. And so once a patient had been	13:28
21	definitively diagnosed with retinitis pigmentosa	13:28
22	at that time, 2007-2008, it was your standard	13:28
23	practice to direct them to take high doses of	13:28
24	vitamin A?	13:28
25	MR. MILLS: Objection. Form.	13:28

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1 THE WITNESS: That's not what I said. I 13:28
2 think -- I said what I said. And that was my 13:29
3 standard practice at the time. I can reiterate it 13:29
4 if you like. 13:29
5 BY MR. FELDSTEIN: 13:29
6 Q. So you had separated in your answer the 13:29
7 patients who were definitively diagnosed versus 13:29
8 not, so I just wanted to be clear. 13:29
9 I'm asking, once a patient had been 13:29
10 definitively diagnosed with retinitis pigmentosa 13:29
11 in the time frame of 2007 to 2008, was it your 13:29
12 standard practice to direct them to take high 13:29
13 doses of vitamin A? 13:29
14 MR. MILLS: Objection. Form. 13:29
15 THE WITNESS: Again, that's sort of not 13:29
16 what I said. But what I said was that I would 13:29
17 typically make a provisional diagnosis and refer 13:29
18 them to the university where Dr. Duncan would make 13:29
19 a definitive diagnosis and would make whatever 13:29
20 recommendation she would make. 13:29
21 I suppose in the hypothetical scenario -- 13:29
22 and I don't know that it ever happened; I can't 13:29
23 remember it ever happening -- where the patient 13:29
24 refused to go to the university, I would have made 13:29
25 these recommendations in accordance with the 13:29

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1	person -- publication.	13:29
2	I suppose in a hypothetical scenario --	13:29
3	which I don't think ever happened, and I can't	13:30
4	remember it ever happening -- where I sent the	13:30
5	patient over to UCSF, and they said, "Gee, I	13:30
6	really didn't like Dr. Duncan, I want you to take	13:30
7	care of me," I probably would have either sent	13:30
8	them to Stanford or UC Davis. Or if they refused	13:30
9	that, I probably would have recommended the	13:30
10	supplements as guided by this publication at that	13:30
11	time.	13:30
12	BY MR. FELDSTEIN:	13:30
13	Q. Have you ever recommended, to your	13:30
14	recollection, high doses of vitamin A to retinitis	13:30
15	pigmentosa patients?	13:30
16	MR. MILLS: Objection. Form.	13:30
17	THE WITNESS: Ever? Probably. I don't	13:30
18	have a specific recollection because of the	13:30
19	practice patterns that I've just identified.	13:30
20	And again, these are not common diseases	13:30
21	either. These are -- these are not -- you know,	13:30
22	these are not super rare, but they're pretty rare.	13:30
23	BY MR. FELDSTEIN:	13:30
24	Q. How would one determine the effective dose	13:30
25	of vitamin A for retinitis pigmentosa? Do you	13:30

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1	have any understanding of that?	13:30
2	A. Well, I think that misunderstands the	13:30
3	literature. The literature really, as I read	13:31
4	it -- and this was the paper that people were	13:31
5	basing their treatment at that time on -- makes a	13:31
6	specific recommendation of 15,000 international	13:31
7	units per day of vitamin A, and they go through	13:31
8	the rationale for that in the -- in the discussion	13:31
9	in terms of avoiding toxicity and achieving some	13:31
10	increase in serum vitamin A levels.	13:31
11	There is not, like, a range of different	13:31
12	doses that they recommend. That's the dose that	13:31
13	they studied. That's the dose they recommend.	13:31
14	They didn't really do a -- they didn't do a	13:31
15	dose-response study. They did look at total	13:31
16	vitamin A intake estimated from diet plus	13:31
17	supplementation, but they didn't really do a	13:31
18	dose-response study, per se.	13:31
19	Q. Would the dose that's disclosed in Berson	13:31
20	be the effective dose for other retinal diseases?	13:31
21	MR. MILLS: Objection to form.	13:32
22	THE WITNESS: I think that would be a	13:32
23	speculation. It may be an informed speculation;	13:32
24	it might be a testable speculation; but it's still	13:32
25	a speculation.	13:32

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1	BY MR. FELDSTEIN:	13:32
2	Q. When did the concept, according to Berson,	13:32
3	Exhibit 1040, to use high doses of vitamin A for	13:32
4	retinitis pigmentosa, when did that fall out of	13:32
5	favor, to your knowledge?	13:32
6	MR. MILLS: Objection to form.	13:32
7	THE WITNESS: I can't give you an exact	13:32
8	date, but I think it was around ten years ago.	13:32
9	But I really can't give you any precision.	13:32
10	BY MR. FELDSTEIN:	13:32
11	Q. Do you know if the results in Berson were	13:32
12	debated or otherwise drawn into question prior to	13:32
13	the time period 2007-2008?	13:32
14	A. Eliot Berson was a very respected doctor,	13:32
15	and this was coming out of Harvard Medical School,	13:32
16	Mass. Eye and Ear Infirmary, which is a very	13:33
17	respected place, and it was a large study. It was	13:33
18	well received at the time, at least at the time	13:33
19	was not challenged.	13:33
20	And my understanding, not having recently	13:33
21	reviewed this later literature, which is after the	13:33
22	priority date, is that others were not able to	13:33
23	replicate these findings in other large	13:33
24	well-designed studies.	13:33
25	Q. What's your basis for saying that the	13:33

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1	Berson results were not challenged at the time?	13:33
2	A. I think I just gave you that answer. It	13:33
3	was a well-respected researcher, a well-respected	13:33
4	institution with a large, well-designed study	13:33
5	reported in a reputable journal, peer-reviewed,	13:33
6	and the data analysis appeared to be solid. So it	13:33
7	was generally accepted at the time.	13:33
8	Q. And what I'm trying to tease out is	13:33
9	whether it's your inference based on Berson's	13:34
10	reputation and such that it was not challenged, or	13:34
11	that you've actually considered the art as of	13:34
12	2007-2008 and know definitively that Berson's	13:34
13	conclusions were not challenged at the time?	13:34
14	A. I have not gone back and systematically	13:34
15	looked at what people were commenting at in 2007	13:34
16	about the specific issue regarding retinitis	13:34
17	pigmentosa.	13:34
18	Q. Have you ever looked at what the	13:34
19	literature in the time frame of 2007-2008 said	13:34
20	regarding the Berston -- Berson results?	13:34
21	MR. MILLS: Objection. Form.	13:34
22	THE WITNESS: So that's a very specific	13:34
23	inquiry. Ever? I might have. Not that I know	13:34
24	of. That was 17 years ago. But I was practicing	13:34
25	at the time, and I do remember practice patterns	13:34

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1	changing when those findings were not replicated.	13:34
2	And I've told you already I don't remember exactly	13:35
3	when that was.	13:35
4	BY MR. FELDSTEIN:	13:35
5	Q. Berson is a reference that you identified	13:35
6	as having previously been aware of?	13:35
7	A. I was aware of it, yes.	13:35
8	Q. And do you recall how you became aware of	13:35
9	Berson in the first place?	13:35
10	A. I read the journal.	13:35
11	Q. The journal is what?	13:35
12	A. Archives of Ophthalmology.	13:36
13	Q. Is that a standard in your field?	13:36
14	A. Well, it's got a new name now, but yes,	13:36
15	it's called JAMA Ophthalmology now.	13:36
16	Q. In the 2007 -- actually, Berston is --	13:36
17	Berson is back in 1993; correct?	13:36
18	A. Correct.	13:36
19	Q. And were you reading it contemporaneously	13:36
20	back in 1993, that journal?	13:36
21	A. Yes.	13:36
22	Q. And were you actually a subscriber to the	13:36
23	journal?	13:36
24	A. Well, I was a resident at the time, so I	13:36
25	was using the university's subscription.	13:36

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1	Q. So you would have read Berson in its	13:36
2	original publication in what is apparently	13:36
3	Volume 111 from June 1993?	13:36
4	A. Yes.	13:36
5	Q. And you weren't aware back then of any	13:36
6	criticisms of Berson?	13:36
7	A. Now you're asking what I remember from	13:36
8	31 years ago?	13:36
9	Q. Correct.	13:36
10	A. Was I aware 31 years ago of any criticisms	13:36
11	of Berson? As we sit here today, I don't recall	13:36
12	being aware 31 years ago of any criticisms of	13:36
13	Berson, which doesn't mean there weren't any and	13:36
14	doesn't mean I didn't know about them at the time.	13:37
15	Q. In this case, you relied on Berson, but	13:37
16	you didn't investigate whether there were	13:37
17	contemporaneous criticisms of Berson; correct?	13:37
18	MR. MILLS: Objection. Form.	13:37
19	THE WITNESS: I cited them. I'm always	13:37
20	wary of the term "rely."	13:37
21	But I think my recollection of that time	13:37
22	period was that this was -- as I've said now a	13:37
23	couple of times -- was well regarded and was	13:37
24	accepted by the field. That doesn't mean that	13:37
25	there weren't people who disagreed. I'm sure it's	13:37

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1	possible that there were, but I don't have any	13:37
2	independent recollection of that.	13:37
3	BY MR. FELDSTEIN:	13:37
4	Q. Sure. I think maybe the question got	13:37
5	lost.	13:37
6	You didn't investigate whether there was	13:37
7	contemporaneous criticism of Berson as part of	13:37
8	preparing and providing your opinions in this	13:37
9	case; correct?	13:37
10	MR. MILLS: Objection to form.	13:37
11	THE WITNESS: That is true.	13:37
12	MR. FELDSTEIN: Thank you.	13:38
13	MR. MILLS: We're coming close to an hour.	13:38
14	If you're moving to a different document, do you	13:38
15	want a break?	13:38
16	MR. FELDSTEIN: Sure. Let me just see	13:38
17	where I am, and I'll tell you in one second.	13:38
18	Let's take a break.	13:38
19	(Recess taken.)	13:38
20	BY MR. FELDSTEIN:	13:38
21	Q. Doctor, can you turn to Exhibit 1028 in	13:53
22	your materials. And, again -- well, not again,	13:53
23	maybe, but if you need copies of anything, let me	13:53
24	know.	13:53
25	A. I'm looking. 1028.	13:54

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1	I think I should read this.	13:54
2	Q. Take your time, Doctor.	13:54
3	A. Thank you.	13:54
4	All right.	14:02
5	Q. You rely on Exhibit 1028 in your	14:02
6	declaration; correct?	14:02
7	A. I cite it.	14:02
8	Q. You cite it, but you don't rely on it --	14:02
9	A. Well --	14:02
10	Q. I'm sorry. Can I finish the question.	14:03
11	You cite Exhibit 1028, but you don't rely	14:03
12	on it? Is that the distinction you're trying to	14:03
13	make?	14:03
14	A. What paragraph are we on?	14:03
15	Q. Paragraph 57.	14:03
16	A. I think -- I'm always wary of the term	14:03
17	"rely" because it implies some kind of	14:03
18	infallibility. So I consulted it. I read it. I	14:03
19	cited it. I considered it. I think it provides	14:03
20	some good perspective on the history of vitamin A.	14:03
21	Q. But you wouldn't say you're relying on it?	14:03
22	A. I try to avoid using the word "rely" with	14:03
23	regard to specific references because I think it	14:03
24	implies some kind of infallibility that doesn't	14:03
25	exist.	14:03

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1	Q. So let me flat-out ask the clear question.	14:03
2	Are you relying on Exhibit 1028 in forming	14:03
3	your opinions in this case?	14:03
4	MR. MILLS: Objection to form. Asked and	14:03
5	answered.	14:03
6	THE WITNESS: I think it would really	14:03
7	depend on how you define the word "rely." It's a	14:03
8	term I try to avoid because it seems to imply some	14:03
9	kind of infallibility.	14:03
10	So I read it. I consulted it. I	14:04
11	considered it. I cited it. I think it's a useful	14:04
12	summary of the history of vitamin A. And I'll	14:04
13	just leave it at that.	14:04
14	BY MR. FELDSTEIN:	14:04
15	Q. Sure. However you use the word "rely," is	14:04
16	it correct that you did not rely on Exhibit 1028?	14:04
17	MR. MILLS: Object to the form. Misstates	14:04
18	the testimony. Asked and answered.	14:04
19	THE WITNESS: I think this is the fifth	14:04
20	time. Let's see if I can try to come up with	14:04
21	something that won't cause you to re-ask the	14:04
22	question.	14:04
23	I try to avoid -- so I don't use the term	14:04
24	"rely" typically with regard to literature	14:04
25	references when I'm writing these reports and	14:04

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1	declarations because I think it implies a certain	14:04
2	infallibility that does not exist.	14:04
3	But this is a reference that I read, I	14:04
4	considered, I cited, and I think it's a good	14:04
5	summary of the history of vitamin A.	14:04
6	BY MR. FELDSTEIN:	14:04
7	Q. I understand what you had said to me, that	14:05
8	you did not necessarily rely on the document.	14:05
9	And what journal is Exhibit 1028 from?	14:05
10	A. This is The FASEB Journal, which is the	14:05
11	Federation of American Societies of Experimental	14:05
12	Biology.	14:05
13	Q. Is this something also that you track in	14:05
14	the ordinary course of your career?	14:05
15	A. I'm aware of it. It's not a major journal	14:05
16	in our area, and it's not something that I read	14:05
17	with regularity.	14:05
18	Q. Is this the type of article, Exhibit 1028,	14:05
19	that clinicians would rely on for making clinical	14:05
20	decisions?	14:05
21	A. I would say this is more of a background	14:05
22	article on the history and the science of vitamin	14:05
23	A and it's not written necessarily with a	14:05
24	clinical, as much as a scientific, perspective.	14:05
25	Q. And first topic in Exhibit 1028 is	14:05

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1	"Vitamin A Deficiency"; correct?	14:05
2	A. Well, it says that.	14:06
3	Q. Is that the correct -- that's the first	14:06
4	topic, Doctor?	14:06
5	A. Well, if I were going to assign a topic	14:06
6	sentence to this, I would say it's more about the	14:06
7	history of -- of treatment. Just as it says in	14:06
8	the main topic, it's a history of vitamin A and	14:06
9	retinoids. It's kind of a history of recognition	14:06
10	and treatment of vitamin A deficiency with an	14:06
11	emphasis on the role of the liver in being a good	14:06
12	source of vitamin A.	14:06
13	Q. So are you disputing that the first major	14:06
14	topic in Exhibit 1028 is about vitamin A	14:06
15	deficiency?	14:06
16	A. I just -- the way you characterize my	14:06
17	responses is so different from what I actually	14:06
18	say. I said what I said.	14:06
19	It's a summary of the history of the	14:06
20	diagnosis and treatment of vitamin A deficiency	14:06
21	from a -- more of a historical standpoint than a	14:06
22	scientific standpoint, although there is some	14:06
23	science in there.	14:06
24	Q. Exhibit 1028 doesn't address lipofuscin	14:06
25	accumulation; correct?	14:07

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1 MR. MILLS: Objection to form. 14:07

2 THE WITNESS: Not directly, no. 14:07

3 BY MR. FELDSTEIN: 14:07

4 Q. And it doesn't direct (sic) age-related 14:07

5 macular degeneration; correct? 14:07

6 MR. MILLS: Objection to form. 14:07

7 THE WITNESS: I don't think it mentions 14:07

8 macular degeneration. 14:07

9 BY MR. FELDSTEIN: 14:07

10 Q. And it doesn't address Stargardt's 14:07

11 disease; correct? 14:07

12 MR. MILLS: Objection to form. 14:07

13 THE WITNESS: I don't believe it mentions 14:07

14 Stargardt's disease. 14:07

15 BY MR. FELDSTEIN: 14:07

16 Q. Okay. Can you turn to Exhibit 1029, which 14:07

17 you cite and -- but maybe not rely on -- I don't 14:07

18 know -- in paragraph 59. 14:07

19 A. I see it. 14:07

20 Q. And Exhibit 1029 is addressing vitamin A 14:07

21 deficiencies; correct? 14:07

22 A. Well, it's specifically addressing the 14:07

23 effects of vitamin A deficiency on the ocular 14:08

24 surface. 14:08

25 And so if we're going to talk about that, 14:08

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1	I'd like to read it.	14:08
2	Q. And here's the question that I'll just put	14:08
3	on the table for you while you're reviewing.	14:08
4	A. Sure.	14:08
5	Q. Exhibit 1029 doesn't address age-related	14:08
6	macular degeneration or Stargardt's disease?	14:08
7	A. Is that your only question? Because if	14:08
8	so, that will expedite my review.	14:08
9	Q. That is my only question.	14:08
10	A. All right. Well, I'm not going to go	14:08
11	through all the references in detail. There might	14:09
12	be something in the references.	14:09
13	But in the body of the article, I don't	14:09
14	see any reference to macular -- was that your	14:09
15	question? Macular disease? Macular --	14:09
16	Q. Macular degeneration or Stargardt's.	14:09
17	A. I did not see a direct reference to either	14:09
18	of those diseases in this paper.	14:09
19	Q. Okay. Can you turn to Exhibit 1037.	14:09
20	A. All right.	14:09
21	Q. And you cite this in paragraph 76 of your	14:09
22	declaration; correct?	14:09
23	A. I see that.	14:09
24	Q. And Exhibit 1020- -- excuse me -- Exhibit	14:09
25	1037 is generally directed to night blindness	14:09

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1	caused by vitamin A deficiencies; correct?	14:09
2	A. So let me just read this, review this	14:10
3	briefly.	14:10
4	So -- let me look at your question again.	14:14
5	So 1037 is directed toward the	14:15
6	mechanism of -- potential mechanism for night	14:15
7	blindness based on the effect of isotretinoin and	14:15
8	tretinoin on cis and trans retinol dehydrogenases	14:15
9	in vitro.	14:15
10	Q. Are you ready for a question, Doctor?	14:16
11	A. Yeah.	14:16
12	Q. Exhibit 1037 doesn't discuss age-related	14:16
13	macular degeneration; correct?	14:16
14	MR. MILLS: Objection to form.	14:16
15	THE WITNESS: I did not see a reference to	14:16
16	that.	14:16
17	BY MR. FELDSTEIN:	14:16
18	Q. Exhibit 1037 doesn't address Stargardt's	14:16
19	disease; correct?	14:16
20	A. I did not see a reference to Stargardt's.	14:16
21	Q. Exhibit 1037 does not address lipofuscin	14:16
22	accumulation; correct?	14:16
23	A. No, it did not mention it, did not mention	14:16
24	lipofuscin.	14:17
25	Q. Can you turn to Exhibit 1041, Doctor.	14:17

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1 A. I'm just looking to see where I mentioned 14:17
2 that. 14:17
3 Q. Paragraph 85, I believe. 14:17
4 A. I see that. 14:17
5 Q. Exhibit 1041 is directed to a disease, 14:17
6 Sorsby's fundus dystrophy; correct? 14:17
7 MR. MILLS: Objection to form. 14:17
8 THE WITNESS: Sorsby's, S-o-r-s-b-y-'-s. 14:17
9 Specifically, it says (as read): 14:17
10 "Night blindness in Sorsby's fundus dystrophy 14:18
11 reversed by vitamin A." 14:18
12 BY MR. FELDSTEIN: 14:18
13 Q. I think you misspelled it. It's 14:18
14 S-o-r-s-b-y-'-s; correct? 14:18
15 A. Well, that's what I meant to say. If I 14:18
16 didn't say that, I apologize. S-o-r-s-b-y-'-s. 14:18
17 Q. And Sorsby's disease is characterized by a 14:18
18 local vitamin A deficiency in the retina; correct? 14:18
19 A. Let me read this. 14:18
20 Q. Let me withdraw the question and ask a 14:18
21 different one. 14:18
22 Do you treat Sorsby's disease, Doctor? 14:18
23 A. So Sorsby's is a very rare disease, and 14:18
24 I'm not sure if I have ever seen a case. And if I 14:18
25 did, I would follow the same management pathway 14:18

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1	that I have outlined earlier in referring them to	14:18
2	a person who is a -- who specializes in retinal	14:18
3	inherited disease at the University of California.	14:19
4	Q. Let me ask my question, and then you can	14:19
5	read, so you know what are looking for.	14:19
6	Sorsby's disease is characterized by a	14:19
7	local vitamin A deficiency in the retina; is that	14:19
8	correct?	14:19
9	A. All right. Give me a moment, please.	14:19
10	So the authors don't quite come to the	14:23
11	definitive statement that you said there, but they	14:23
12	do say this (as read):	14:23
13	"We have administered supplemental vitamin A to SFD	14:23
14	patients with a novel TIMP3 mutation and monitored	14:23
15	their visual function to test the hypothesis that at	14:23
16	least part of the visual disturbance in SFD may be	14:23
17	due to a form of nutritional deprivation at the level	14:23
18	of the photoreceptor. The restoration of broad	14:23
19	visual function to normal while on supplemental	14:23
20	vitamin A in some of these patients supports the	14:23
21	hypothesis."	14:23
22	That's what they say.	14:23
23	Q. Exhibit 1041 isn't directed to the	14:23
24	treatment of macular degeneration; correct?	14:23
25	MR. MILLS: Objection to form.	14:23

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1	THE WITNESS: Well, so it's not directed	14:23
2	to the treatment of age-related macular	14:23
3	degeneration. It's directed toward the treatment	14:24
4	of Sorsby's fundus dystrophy, which is a different	14:24
5	type of degeneration.	14:24
6	BY MR. FELDSTEIN:	14:24
7	Q. And Exhibit 1041 is not directed to	14:24
8	Stargardt's disease; correct?	14:24
9	MR. MILLS: Objection to form.	14:24
10	THE WITNESS: They don't mention	14:24
11	Stargardt's anywhere in the text that I can see.	14:24
12	BY MR. FELDSTEIN:	14:24
13	Q. And Exhibit 1041 is not directed to the	14:24
14	lipofuscin accumulation; correct?	14:24
15	MR. MILLS: Objection to form.	14:24
16	THE WITNESS: So they do mention some	14:24
17	abnormal material that forms in the retina, but in	14:24
18	this study, all the testing was done on live	14:24
19	humans, and no tissue samples were obtained, and I	14:24
20	don't believe they commented on or analyzed for	14:24
21	presence or absence of lipofuscin.	14:24
22	BY MR. FELDSTEIN:	14:24
23	Q. You may have covered this earlier, but	14:24
24	Stargardt's disease is not caused by vitamin A	14:24
25	deficiencies; correct?	14:24

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1 MR. MILLS: Objection to form. 14:24

2 THE WITNESS: I would generally agree with 14:25

3 that. 14:25

4 BY MR. FELDSTEIN: 14:25

5 Q. And age-related macular degeneration is 14:25

6 also not caused by vitamin A deficiency; correct? 14:25

7 MR. MILLS: Objection to form. 14:25

8 THE WITNESS: I think that's generally -- 14:25

9 that would generally be accepted. 14:25

10 BY MR. FELDSTEIN: 14:25

11 Q. Can you turn to Exhibit 1042. It's cited 14:25

12 in paragraph 86 of your declaration. 14:25

13 A. Okay. 14:25

14 Q. Exhibit 1042 is not directed to 14:25

15 age-related macular degeneration; correct? 14:25

16 MR. MILLS: Objection to form. 14:25

17 THE WITNESS: Let me read the article 14:25

18 again and just take a look to make sure that is 14:25

19 not mentioned. 14:25

20 I do not see a reference to age-related 14:26

21 macular degeneration in the article. 14:26

22 BY MR. FELDSTEIN: 14:26

23 Q. And Exhibit 1042 is not directed to 14:26

24 Stargardt's disease; correct? 14:26

25 A. I did not -- 14:26

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1	MR. MILLS: Objection. Form.	14:26
2	THE WITNESS: I did not see a mention of	14:26
3	Stargardt's disease.	14:26
4	BY MR. FELDSTEIN:	14:26
5	Q. And Exhibit 1042 is not directed to	14:27
6	lipofuscin accumulation; correct?	14:27
7	MR. MILLS: Objection. Form.	14:27
8	THE WITNESS: Let me just verify that.	14:27
9	I don't see any data about lipofuscin.	14:27
10	BY MR. FELDSTEIN:	14:27
11	Q. Can you turn to Exhibit 1043, which you	14:27
12	cite in paragraph 87 of your declaration.	14:27
13	A. If you can ask me your question, that will	14:27
14	expedite my review.	14:27
15	Q. Sure. They're very similar, but I will	14:27
16	also ask, Exhibit 1043 is directed to	14:27
17	recommendations for vitamin A supplementation in	14:27
18	patients with vitamin A deficiencies; is that	14:28
19	correct?	14:28
20	MR. MILLS: Objection to form.	14:28
21	THE WITNESS: Well, it's directed	14:28
22	primarily toward vitamin A supplementation in	14:28
23	infants, children, pregnant and postpartum women,	14:28
24	and with an eye toward preventing and treating	14:28
25	vitamin A deficiency.	14:28

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1	BY MR. FELDSTEIN:	14:28
2	Q. And Exhibit 1043 is not directed to	14:28
3	treating age-related macular degeneration	14:28
4	patients; correct?	14:28
5	MR. MILLS: Objection to form.	14:28
6	THE WITNESS: So although the authors do	14:29
7	reference the response of the retina to treatment	14:29
8	with night blindness and poor dark adaptation	14:29
9	often persisting for at least four weeks and they	14:29
10	also discuss vision loss in women, they do not	14:29
11	discuss age-related macular degeneration.	14:29
12	BY MR. FELDSTEIN:	14:29
13	Q. And Exhibit 1043 is not directed to	14:29
14	treating Stargardt's disease; correct?	14:29
15	MR. MILLS: Objection to form.	14:29
16	THE WITNESS: So although they do mention	14:29
17	that the retina is usually the slowest to respond	14:29
18	to treatment with night blindness and poor dark	14:29
19	adaptation often persisting for at least four	14:30
20	weeks and they mention blindness with vitamin A	14:30
21	deficiency, they do not appear to mention	14:30
22	Stargardt's disease.	14:30
23	BY MR. FELDSTEIN:	14:30
24	Q. And Exhibit 1043 is not directed to	14:30
25	reducing lipofuscin accumulation; correct?	14:30

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1	MR. MILLS: Objection to form.	14:30
2	THE WITNESS: So although they do mention	14:30
3	that the retina is usually the slowest to respond	14:30
4	to treatment with night blindness and poor dark	14:30
5	adaptation often persisting for at least four	14:30
6	weeks and they do mention blindness in women with	14:30
7	vitamin A deficiency, they do not directly address	14:30
8	lipofuscin accumulation.	14:30
9	BY MR. FELDSTEIN:	14:30
10	Q. Is there some reason, Doctor, you keep	14:30
11	giving the same canned preamble to -- before	14:30
12	agreeing that they don't discuss age-related	14:31
13	macular degeneration, Stargardt's disease, or	14:31
14	reducing lipofuscin accumulation?	14:31
15	MR. MILLS: Just going to object to the	14:31
16	question as mischaracterizing testimony and is	14:31
17	argumentative.	14:31
18	THE WITNESS: I want to make sure that my	14:31
19	answers are complete.	14:31
20	BY MR. FELDSTEIN:	14:31
21	Q. Can we turn for Exhibit 1025, which I	14:31
22	believe you cite in paragraph 58.	14:31
23	A. Okay.	14:32
24	Q. Exhibit 1025 doesn't discuss treating	14:32
25	age-related macular degeneration; correct?	14:32

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1	MR. MILLS: Objection to form.	14:32
2	THE WITNESS: I'm going to review the	14:32
3	article.	14:32
4	So Exhibit 1025 discusses vitamin A, which	14:34
5	they define as including retinol, retinyl	14:34
6	palmitate, and the provitamin A carotinoids, such	14:34
7	as all-trans-beta- carotene, and they do discuss	14:34
8	nightblindness cured by animal liver, but they	14:34
9	otherwise focus on the epithelium of the eye and	14:34
10	other target tissues in the body and not on	14:34
11	age-related macular degeneration.	14:34
12	BY MR. FELDSTEIN:	14:34
13	Q. And I expect you're probably going to	14:34
14	repeat that same preamble again, but can you,	14:34
15	whether you do that or not, confirm that	14:34
16	Exhibit 1025 doesn't discuss treating Stargardt's	14:34
17	disease?	14:35
18	MR. MILLS: Objection. Form.	14:35
19	THE WITNESS: I did not see a reference to	14:35
20	Stargardt's disease.	14:35
21	BY MR. FELDSTEIN:	14:35
22	Q. And can you confirm that Exhibit 1025	14:35
23	doesn't address reducing lipofuscin accumulation?	14:35
24	A. I did not see a reference to lipofuscin	14:35
25	accumulation.	14:35

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1	Q. We'll move on to Exhibit 1053, which I	14:35
2	believe you cite in paragraph 89.	14:35
3	A. Okay.	14:35
4	Q. Now, without getting into a fight on	14:35
5	whether you, quote, relied on it or merely, quote,	14:35
6	cited it, what is your purpose for having included	14:35
7	Exhibit 1053 in your declaration?	14:35
8	A. Give me a moment, please. We're on are	14:35
9	paragraph 89?	14:36
10	Q. Correct.	14:36
11	A. So without trying to be disrespectful, I	14:36
12	think paragraph 89 speaks for itself.	14:36
13	I cited this study because it shows an	14:36
14	example of deuterated vitamin A in corn oil being	14:36
15	administered to elderly patients for -- an assay	14:36
16	of vitamin A by the deuterated-retinol-dilution	14:36
17	method. That was the intent of the citation.	14:37
18	Q. A person of ordinary skill wouldn't rely	14:37
19	on Exhibit 1053 to conclude that deuterated	14:37
20	retinyl acetate is safe and effective for the	14:37
21	treatment of any disease; do you agree with that?	14:37
22	MR. MILLS: Objection to form.	14:37
23	THE WITNESS: I think that the paper does	14:37
24	provide some information on safety, but it does	14:37
25	not provide any information on effectiveness and	14:37

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1	treatment of any disease.	14:37
2	BY MR. FELDSTEIN:	14:37
3	Q. And this was a single-dose study; is that	14:37
4	correct?	14:37
5	A. Let me just review this again.	14:37
6	Q. Take your time, Doctor.	14:37
7	A. Thank you.	14:37
8	My understanding is that there was a	14:40
9	single dose of the deuterated vitamin A that was	14:40
10	administered.	14:40
11	Q. And it was a single dose of 0.015	14:40
12	millimoles; is that correct?	14:41
13	A. That's what it says.	14:41
14	Q. And in your opinion, would a person of	14:41
15	ordinary skill rely on a single dose of 0.015	14:41
16	millimole of deuterated retinyl acetate to infer	14:41
17	anything about safety and efficacy of that	14:41
18	compound for the treatment of the disease?	14:41
19	MR. MILLS: Objection to form.	14:41
20	THE WITNESS: So I think it's a piece of	14:41
21	information, and this is not the only study	14:41
22	involving administration of deuteration --	14:41
23	deuterated vitamin A compounds, Olson '89 being	14:42
24	another -- Olson 1989 being another example.	14:41
25	And I think a POSA would have been	14:41

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1 reassured by the absence of reported adverse 14:41
2 effects or events but would not necessarily infer 14:41
3 that a -- that a drug that, presumably, would be 14:42
4 administered repeatedly would necessarily be safe 14:42
5 for long-term use without the type of routine 14:42
6 clinical trials that people do to establish safety 14:42
7 and efficiency. 14:42
8 BY MR. FELDSTEIN: 14:42
9 Q. And at the end of paragraph 89 of your 14:42
10 report, you specify the name of the deuterated 14:42
11 compound in more detail, 14:42
12 "(all-trans-retinyl-10,19,19,19-[2H-" -- 14:42
13 A. -- "[2H4]acetate) in corn oil." 14:42
14 I'm reading the same passage you are. 14:42
15 Q. What are the numbers 10, 19, 19, and 19 14:42
16 referring to, Doctor? 14:42
17 A. So this is a d4-substituted compound. In 14:42
18 other words, there are deuterium atoms at 14:43
19 carbon-10, and there are three deuterium atoms on 14:43
20 carbon-19. 14:43
21 Q. And do you have an understanding why this 14:43
22 deuterated retinyl acetate was used in the study 14:43
23 in example 1053 -- Exhibit 1053? 14:43
24 MR. MILLS: Objection. Form and scope. 14:43
25 THE WITNESS: I would have to go back to 14:43

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1	the Olson references, but my general understanding	14:43
2	is that this is used as a tracer. And so the	14:43
3	design of the deuteration is so as to avoid	14:43
4	effects on its metabolism.	14:43
5	BY MR. FELDSTEIN:	14:43
6	Q. Turn to Exhibit 1040- -- whoops -- 10- --	14:43
7	A. We are coming up on another hour here.	14:43
8	MR. MILLS: Yeah, if we are going to a new	14:43
9	exhibit, maybe we can take a break.	14:44
10	MR. FELDSTEIN: Let's go on a break.	14:44
11	Going off the record.	14:44
12	(Recess taken.)	14:44
13	BY MR. FELDSTEIN:	15:02
14	Q. Can you turn to Exhibit 1044 and	15:02
15	paragraph 90 in your declaration.	15:02
16	In paragraph 90, you -- the last four	15:03
17	lines, you quote the abstract of Exhibit 1044;	15:03
18	correct?	15:03
19	A. I see that.	15:03
20	Q. And you quote it as administering (as	15:03
21	read):	15:03
22	"Two oral doses of [2H4]-retinyl acetate [52.4	15:03
23	millimolar]"; correct?	15:03
24	A. I think it's "millimole retinol	15:03
25	equivalents."	15:03

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1	Q. Okay. I think it's micromole, isn't it,	15:03
2	if you look at 1044 --	15:03
3	A. Looking at the original, you are correct.	15:03
4	It is micromole. So that's an error.	15:03
5	Q. The doses were actually a thousand times	15:03
6	smaller than what you list in paragraph 90;	15:03
7	correct?	15:03
8	A. Yeah. A micromole is 1/1000th of a	15:03
9	millimole.	15:04
10	Q. And in your opinion, would a person of	15:04
11	ordinary skill have relied on the two	15:04
12	52.4-micromolar doses of deuterated retinyl	15:04
13	acetate to extrapolate any safety or efficacy of	15:04
14	that compound for the treatment of a disease?	15:04
15	A. So similar to your previous question, this	15:04
16	is a piece of information. In this case, we have	15:04
17	two doses...	15:04
18	Let me just look and review this a little	15:04
19	bit more here.	15:04
20	So it provides information that no safety	15:04
21	signal was detected in terms of adverse events	15:04
22	after administering these two doses.	15:05
23	In terms of providing information for	15:05
24	treatment of a disease with, presumably, ongoing	15:05
25	dosing, it would suggest that it may well be safe,	15:05

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1	but routine testing in terms of clinical trials	15:05
2	would be needed to establish the safety of	15:05
3	repeated dosing, and it provides no information	15:05
4	with regard to efficacy of treatment of a disease.	15:05
5	Q. Can we turn now to Exhibit 1045, which you	15:05
6	cite in paragraph 93.	15:05
7	And my question, as you orient yourself,	15:05
8	is: Can you confirm -- well, let me try again.	15:05
9	In your opinion, would a person of	15:05
10	ordinary skill have relied on Exhibit 1045 to	15:05
11	extrapolate any safety or efficacy of the	15:06
12	administered compound for the treatment of a	15:06
13	disease?	15:06
14	A. So the -- in my opinion, a POSA would find	15:06
15	this to be a data point indicating safety, with	15:06
16	the absence of a safety signal or adverse event,	15:06
17	from a single-dose administration of this	15:06
18	deuterated compound and would have, obviously, not	15:06
19	concluded just on the basis of this data point	15:06
20	that repeated administration would be safe but	15:06
21	would need to do routine experimentation in the	15:06
22	form of clinical trials to establish the safety of	15:06
23	repeated dosing, and a POSA would not draw	15:07
24	conclusions about efficacy of treatment of any	15:07
25	disease using this particular dataset.	15:07

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1	Q. Does Exhibit 1045 identify where the	15:07
2	molecule is deuterated?	15:07
3	A. Yes. And it is 10,19,19,19-deuterium	15:07
4	retinyl, r-e-t-i-n-y-l.	15:07
5	Q. I'm sorry. Where are you reading?	15:07
6	A. I'm on page 68. 10,19,19,19-deuterium	15:07
7	retinyl, r-e-t-i-n-y-l, acetate in corn oil.	15:07
8	Q. And do you have an understanding of why	15:07
9	that specific deuteration was used in Exhibit --	15:07
10	the study that is Exhibit 1045?	15:07
11	MR. MILLS: Objections as to form and	15:07
12	scope.	15:08
13	THE WITNESS: Yeah, so I haven't -- we can	15:08
14	look back at the Olson references, but my	15:08
15	understanding is that this is used as a tracer and	15:08
16	that those deuterium -- those are the carbons on	15:08
17	which the deuterium atoms are placed and that this	15:08
18	was chosen in order to not affect the metabolism	15:08
19	of the molecule.	15:08
20	BY MR. FELDSTEIN:	15:08
21	Q. Why don't we actually turn to Olson, as	15:08
22	you suggested, Exhibit 1006.	15:08
23	And just for --	15:08
24	A. Well, this is different from the one I was	15:08
25	looking for.	15:08

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1	Q. Okay. We'll start with this one anyhow,	15:08
2	if that's okay with you.	15:08
3	A. It's your deposition. Give me a moment,	15:08
4	please.	15:08
5	All right.	15:10
6	Q. My first question is: Why do you refer to	15:10
7	this paper, Exhibit 1006, as Olson 1988 instead of	15:10
8	Bergen 1988?	15:10
9	I can direct you to page 53 of your	15:10
10	declaration if you're not sure.	15:10
11	A. No, I'm with you.	15:10
12	I think the intent here was to basically	15:10
13	highlight the similar authorship of what we	15:10
14	have -- what we're calling -- and I believe	15:10
15	Dr. Guengerich calls it the same thing -- Olson	15:10
16	1988 and Olson 1999, which is Exhibit 1007, even	15:10
17	though they have different first authors.	15:11
18	My understanding is that Olson was the	15:11
19	senior author.	15:11
20	Q. And that's contrary to convention, to use	15:11
21	the final author of an article to identify it,	15:11
22	isn't it?	15:11
23	MR. MILLS: Objection to form.	15:11
24	THE WITNESS: I've seen it done both ways.	15:11
25	BY MR. FELDSTEIN:	15:11

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1 Q. So you think it's convention to use the 15:11
2 final author when identifying a reference? 15:11
3 MR. MILLS: Objection to form. 15:11
4 THE WITNESS: I think it depends on whose 15:11
5 convention. Among scientists, it's frequent to 15:11
6 use either the first or the last author. 15:11
7 Typically, the last author is the head of the 15:11
8 laboratory and the person who supervised the 15:11
9 research, and typically, the first person is the 15:11
10 post-doc or graduate student who did the research, 15:11
11 although that can vary. 15:11
12 BY MR. FELDSTEIN: 15:11
13 Q. And with the exception of Exhibits 1006 15:11
14 and 1007, every other time you used a single 15:11
15 author's name, you used the first author; correct? 15:12
16 MR. MILLS: Objection to form. 15:12
17 And caution not to speculate. 15:12
18 THE WITNESS: I would have to go through 15:12
19 all of the references in order to answer that 15:12
20 definitively. But off the top of my head, I don't 15:12
21 remember any others that I used or Dr. Guengerich 15:12
22 used anything other than the first author. 15:12
23 BY MR. FELDSTEIN: 15:12
24 Q. Now, Exhibit 1006 in the summary refers to 15:12
25 biological studies of vitamin A metabolism. 15:12

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1	Do you see that?	15:12
2	A. I'm sorry. Where are we now?	15:12
3	Q. In the summary, sort of the abstract of	15:12
4	Exhibit 1006, last -- the end of the first	15:12
5	paragraph.	15:12
6	A. Oh, okay. I see that.	15:12
7	Q. What is your understanding of the	15:12
8	biological studies that are being addressed in	15:12
9	Exhibit 1006?	15:13
10	MR. MILLS: Objection to form and scope.	15:13
11	THE WITNESS: My understanding is that	15:13
12	this is generally used in dilution -- isotope	15:13
13	dilution studies.	15:13
14	BY MR. FELDSTEIN:	15:13
15	Q. And do you understand what the	15:13
16	requirements are, if any, for deuterated molecules	15:13
17	for use in isotope dilution studies?	15:13
18	MR. MILLS: Objections to form and scope	15:13
19	and to the extent the question calls for	15:13
20	speculation.	15:13
21	THE WITNESS: As a clinician, I understand	15:13
22	that these molecules are expected to be -- or	15:13
23	should be safe when administered in these types of	15:13
24	studies.	15:13
25	And the team -- the Bergen, Furr, and	15:13

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1	Olson team that wrote this talked about the	15:13
2	prevalence of carbon-13 in this 20-carbon compound	15:13
3	being 22 percent. And so in order to have a	15:14
4	detectable mass difference, they recommended	15:14
5	deuteration of three or more deuteriums.	15:14
6	And then, finally, if you are doing this	15:14
7	type of study, my understanding is that you want	15:14
8	to have a molecule that's going to behave	15:14
9	chemically similar to the original molecule.	15:14
10	BY MR. FELDSTEIN:	15:14
11	Q. In other words, you want the deuterium	15:14
12	substitutions not to affect the biochemistry of	15:14
13	the molecule; is that correct?	15:14
14	MR. MILLS: Objection as to form.	15:14
15	THE WITNESS: So it's going to depend on,	15:14
16	you know, the specific biochemistry in different	15:14
17	contexts and/or tissues and/or reactions. But	15:14
18	generally speaking, my understanding is that that	15:14
19	is the goal of this synthesis.	15:14
20	BY MR. FELDSTEIN:	15:14
21	Q. And Exhibit 1006 is towards studies of	15:14
22	vitamin A metabolism; is that correct?	15:14
23	A. Well, that's what it says.	15:15
24	Q. And Exhibit 1006 isn't directed to	15:15
25	treating any diseases; correct?	15:15

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1	MR. MILLS: Objection to form.	15:15
2	THE WITNESS: I did not see anything in	15:15
3	the paper that talked about treating a disease.	15:15
4	BY MR. FELDSTEIN:	15:15
5	Q. Do you understand from Exhibit 1006	15:15
6	whether any particular deuterated vitamin A	15:15
7	species was preferred?	15:15
8	MR. MILLS: Objection to form, scope.	15:15
9	THE WITNESS: So they describe the	15:15
10	preparation of some specific molecules, but I	15:15
11	didn't see a lot of commentary, if any, on --	15:15
12	other than they say (as read):	15:15
13	"The most useful for biological studies is the	15:15
14	10,19,19-deuterium for labeled compound."	15:15
15	That was the -- that was the extent of the	15:16
16	commentary, other than saying -- and I'll quote --	15:16
17	this is on the first page of the article (as	15:16
18	read):	15:16
19	"Deuterated compounds should contain three or more	15:16
20	deuteriums in metabolically and chemically stable	15:16
21	positions to provide adequate analytical	15:16
22	sensitivity."	15:16
23	And that's for studying the metabolism of	15:16
24	vitamin A in humans.	15:16
25	BY MR. FELDSTEIN:	15:16

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1 Q. On 2, the last -- first paragraph, last 15:16
2 sentence says (as read): 15:16
3 "The most useful for biological studies is the 15:16
4 10,19,19,19-deuterated labeled compound"; correct? 15:16
5 A. I already said that, yeah, and I'll say it 15:16
6 again. Yes, it says that. 15:16
7 Q. And do you have an understanding of why -- 15:16
8 let me start again. 15:16
9 Why would a person -- what would a person 15:16
10 understand as to why that species is the most 15:17
11 useful for biological studies? 15:17
12 MR. MILLS: Objections to form, scope, and 15:17
13 to the extent the question calls for speculation. 15:17
14 THE WITNESS: I think we're -- you know, 15:17
15 we're approaching more Dr. Guengerich's area of 15:17
16 expertise here. And so in terms of my knowledge 15:17
17 and what the paper says, there's not a lot here. 15:17
18 My understanding is that they state that 15:17
19 deuterated compounds should contain three or more 15:17
20 deuteriums in metabolically and chemically stable 15:17
21 positions to provide adequate analytical 15:17
22 sensitivity, and they state that this 10,19,19,19 15:17
23 molecule is the preferred analog for biological 15:17
24 studies. And they don't go into a lot of detail 15:17
25 on that. 15:17

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1	So beyond citing what they say, I think	15:17
2	I'll refrain from speculation.	15:18
3	BY MR. FELDSTEIN:	15:18
4	Q. Do you have an understanding of what	15:18
5	differences there are, if any, between a C20-D1-3	15:18
6	retinoid and the 10,19,19,19 species we are	15:18
7	discussing from Exhibit 1006?	15:18
8	MR. MILLS: Objections to form, scope, and	15:18
9	to the extent the question calls for speculation.	15:18
10	THE WITNESS: So I think this is a	15:18
11	question that would be better directed to	15:18
12	Dr. Guengerich.	15:18
13	But my understanding from his declaration	15:18
14	and from some of the prior art that's cited in my	15:18
15	report, including Mata and Fishkin, that the C20	15:18
16	position is involved in the formation of harmful	15:18
17	lipofuscin precursors and that the C19 position	15:18
18	either is not involved or plays a much less	15:18
19	important role in those reactions.	15:19
20	BY MR. FELDSTEIN:	15:19
21	Q. Can we turn to Exhibit 1007. This is what	15:19
22	you call Olson 1989; correct?	15:19
23	A. Yes.	15:19
24	Q. And what compound is used in Olson 1989?	15:19
25	A. Give me a moment.	15:21

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1	So they gave 45 milligrams of all-trans	15:21
2	10,19,19,19-deuterium retinol, r-e-t-i-n-o-l, as	15:21
3	retinyl, r-e-t-i-n-y-l, acetate in corn oil as a	15:21
4	single dose.	15:21
5	Q. And Olson 1989 doesn't disclose the use of	15:21
6	that compound for treatment of any disease;	15:21
7	correct?	15:21
8	A. I did not see anything in there related to	15:21
9	treatment of a disease other than -- well, I would	15:21
10	say diagnosis of vitamin A deficiency but not	15:21
11	treatment.	15:21
12	Q. Can we turn to Exhibit 1005, which is your	15:21
13	CV.	15:21
14	It is dated December 13, 2023. Is there	15:21
15	anything materially absent?	15:21
16	A. So I have some additional roles --	15:21
17	teaching and administrative roles at California	15:22
18	Pacific Medical Center.	15:22
19	Let's see.	15:22
20	So in addition to being clinical faculty	15:22
21	and core faculty in ophthalmology at California	15:22
22	Pacific Medical Center, which I'll call CPMC, I am	15:22
23	also the resident and faculty performance lead, I	15:22
24	am the chair of the Clinical Competency Committee,	15:22
25	and I was granted by the residents the Excellence	15:22

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1	in Teaching award this year.	15:22
2	Q. Your list of publications that begins on	15:22
3	an unnumbered page in here --	15:22
4	A. I have no new publications. I have a	15:23
5	couple of new research studies with Carl Zeiss.	15:23
6	Everything else should be the same.	15:23
7	Q. And the publications, you list 21	15:23
8	publications; correct?	15:23
9	A. I would have to count them.	15:23
10	Q. Well, they're numbered.	15:23
11	A. You're right. Yes.	15:23
12	Q. And they range from 1982 through 2017;	15:23
13	correct?	15:23
14	A. Yeah.	15:23
15	Q. And are they all peer-reviewed scientific	15:23
16	publications?	15:23
17	A. So some of them are policy and not -- and	15:23
18	some of them -- I think there may be at least some	15:23
19	that are abstracts.	15:23
20	Q. Which ones are abstracts?	15:23
21	A. Let's look.	15:23
22	Well, Number 1 is a book chapter, so it	15:23
23	would have been reviewed by the editor.	15:23
24	2 is peer-reviewed.	15:23
25	3 is peer-reviewed.	15:23

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1	4 is peer-reviewed.	15:23
2	5 is peer-reviewed.	15:23
3	6 is peer-reviewed.	15:23
4	7 is a book chapter, which would have been	15:23
5	reviewed by the editors.	15:23
6	8 is -- I'm not sure if that -- I'm not	15:23
7	sure if that was a book chapter or that went	15:24
8	through journal peer review.	15:24
9	9 was peer-reviewed.	15:24
10	10, same thing; I think that probably was	15:24
11	a book chapter.	15:24
12	11 was peer-reviewed.	15:24
13	12 --	15:24
14	Q. 11, is that not an abstract? Is that an	15:24
15	article?	15:24
16	A. That is an article.	15:24
17	Q. Okay.	15:24
18	A. It's the proceedings of the National	15:24
19	Academy of Sciences.	15:24
20	Number 12 was a book chapter.	15:24
21	Number 13 was an article, a peer-reviewed	15:24
22	article.	15:24
23	14 was a policy article.	15:24
24	15, 16, 17, those are all policy articles.	15:24
25	And they went through editorial review, but it's	15:24

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1	not a scientific publication.	15:24
2	18 was peer-reviewed.	15:24
3	19 was a policy article.	15:24
4	20 was a policy article.	15:24
5	21 was peer-reviewed.	15:24
6	Q. And on the next page, you have your	15:25
7	clinical research?	15:25
8	A. Yeah.	15:25
9	Q. I'm sure there is infinite levels of	15:25
10	detail here, but generally, the first three, are	15:25
11	they related to diabetes?	15:25
12	A. Yes.	15:25
13	Q. And the rest on that page, are they	15:25
14	related to glaucoma?	15:25
15	A. Yes.	15:25
16	Q. And on the next page, what is the first	15:25
17	one directed to?	15:25
18	A. The first one was primarily monitoring for	15:25
19	ocular side effects for a systemic drug.	15:25
20	Q. And then the rest are directed to imaging	15:25
21	systems?	15:25
22	A. Generally, yes.	15:25
23	The Heru is not imaging. It's a virtual	15:25
24	reality headset that can be used for a variety of	15:25
25	different types of evaluation.	15:25

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1	MR. FELDSTEIN: We'll mark as Exhibit 2071	15:25
2	a page entitled "Andrew F. Calman, M.D., Ph.D.	15:26
3	Contact this Expert Witness" -- capital S-E-A-K --	15:26
4	"Inc."	15:26
5	(Whereupon, Exhibit 2071 was marked for	15:26
6	identification.)	15:26
7	MR. MILLS: I'm going to object to	15:26
8	Exhibit 2071 under Federal Rules of Evidence 901,	15:26
9	801 through 803, 602, 401 through 403.	15:27
10	BY MR. FELDSTEIN:	15:27
11	Q. Doctor, is Exhibit 2071 a web page -- a	15:27
12	printout of a web page disclosing you as an expert	15:27
13	witness available for hire?	15:27
14	A. It --	15:27
15	MR. MILLS: Objection. Foundation.	15:27
16	THE WITNESS: It appears to be a -- it	15:27
17	appears to be a page from SEAK directory regarding	15:27
18	my expert witness qualifications. SEAK is	15:27
19	S-E-A-K.	15:27
20	BY MR. FELDSTEIN:	15:28
21	Q. I take it you're familiar with SEAK,	15:28
22	S-E-A-K; is that correct?	15:28
23	A. I am.	15:28
24	Q. And is it true that you pay for this	15:28
25	listing in SEAK?	15:28

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1	A. I do.	15:28
2	Q. And did you write this listing for SEAK?	15:28
3	A. I did.	15:28
4	Q. And is the listing of expertise that you	15:28
5	wrote accurate, Doctor?	15:28
6	MR. MILLS: Objection. Form.	15:28
7	THE WITNESS: What are we looking at now?	15:28
8	BY MR. FELDSTEIN:	15:28
9	Q. You have "Specialties & Experience of this	15:28
10	Witness."	15:28
11	A. Well, these are some of the search terms	15:28
12	that are selected for people trying to find	15:28
13	ophthalmology experts for various things. But,	15:28
14	yes, I wrote this.	15:28
15	Q. So you put yourself out there as an expert	15:28
16	available to address antitrust issues?	15:29
17	A. I have worked on antitrust cases. It	15:29
18	doesn't mean I'm an antitrust attorney.	15:29
19	Q. I don't think I asked you if you are an	15:29
20	antitrust attorney. Did you misunderstand my	15:29
21	question?	15:29
22	MR. MILLS: Objection. Argumentative.	15:29
23	THE WITNESS: Apparently, I misunderstood	15:29
24	your question.	15:29
25	BY MR. FELDSTEIN:	15:29

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1 Q. So my question was really simple. You put 15:29
2 yourself out there as an expert available to 15:29
3 address antitrust issues; is that correct? 15:29
4 A. I don't think that's a correct 15:29
5 interpretation. I included that in the keywords 15:29
6 and search terms so that attorneys working on 15:29
7 antitrust cases involving ophthalmology would find 15:29
8 me as someone who has worked on similar cases. 15:29
9 Q. And what about "coding"? What does 15:29
10 "coding" refer to? 15:29
11 A. So I used to teach the ophthalmology CPT 15:29
12 coding courses for the American Academy of 15:29
13 Ophthalmology. And sometimes cases come up where 15:29
14 doctors are accused of miscoding their patient 15:29
15 encounters, and I have worked on those cases. And 15:29
16 so for attorneys who are looking for experts who 15:30
17 are familiar with coding cases, I include that as 15:30
18 a search term so they can find me. 15:30
19 Q. So you're offering to testify on coding 15:30
20 issues; is that correct? 15:30
21 MR. MILLS: Objection to form. 15:30
22 THE WITNESS: Well, I'm not sure I've ever 15:30
23 actually had to testify, but I have worked on 15:30
24 cases involving coding for ophthalmologists and 15:30
25 optometrists. 15:30

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1	BY MR. FELDSTEIN:	15:30
2	Q. And "reimbursements," what do you mean by	15:30
3	that?	15:30
4	A. That's -- similarly, when doctors are	15:30
5	accused of improper coding, the corollary to that	15:30
6	is that they have been reimbursed by the insurance	15:30
7	companies incorrectly. And so I have worked on	15:30
8	those types of cases. It's just a search term so	15:30
9	they can find an expert with experience in those	15:30
10	areas.	15:30
11	Q. And you're offering to provide your	15:30
12	testifying experience in the area of ophthalmology	15:30
13	reimbursement; is that correct?	15:30
14	MR. MILLS: Objection to form.	15:30
15	THE WITNESS: Well, I have never actually	15:30
16	had to testify in any of those types of cases, but	15:30
17	I've certainly offered my expertise, and if called	15:30
18	upon to testify, I would.	15:31
19	BY MR. FELDSTEIN:	15:31
20	Q. And in terms of your general specialties	15:31
21	and the keywords, you don't include "age-related	15:31
22	macular degeneration"; correct?	15:31
23	MR. MILLS: Objection to form.	15:31
24	THE WITNESS: Well, I see "macula" and	15:31
25	"retina," but I don't see "age-related macular	15:31

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1	degeneration."	15:31
2	BY MR. FELDSTEIN:	15:31
3	Q. You don't see it because you didn't	15:31
4	include it when you prepared this; correct?	15:31
5	MR. MILLS: Objection to form.	15:31
6	Argumentative.	15:31
7	THE WITNESS: Well, there's a limit to how	15:31
8	many you can put. I put "macula," and I did not	15:31
9	put "age-related macular degeneration."	15:31
10	BY MR. FELDSTEIN:	15:31
11	Q. And between your "General Specialties" and	15:31
12	"Keywords/Search Terms," you didn't identify	15:31
13	"Stargardt's disease" as an area of your	15:31
14	specialties and experience; correct?	15:31
15	MR. MILLS: Objection to form.	15:31
16	THE WITNESS: That's a very narrow term,	15:31
17	and there is a limit to how many terms you can	15:31
18	list. So I did not include that because, for one	15:31
19	thing, it's subsumed under "retina" and "macula,"	15:31
20	and for another, it's a rare disease.	15:31
21	BY MR. FELDSTEIN:	15:31
22	Q. What is the limit on the number of terms	15:31
23	you can use in the keyword search, Doctor?	15:31
24	A. I think it's 20.	15:32
25	Q. Okay. I count 17 in your list. Did I	15:32

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1	count right?	15:32
2	A. I'll take your word for it.	15:32
3	Q. Okay. And am I correct that in your	15:32
4	"Specialties & Experience" that you advertise on	15:32
5	this SEAK web page, you don't identify anything	15:32
6	about "lipofuscin accumulation"? Correct?	15:32
7	MR. MILLS: Objection to form.	15:32
8	THE WITNESS: I would be really	15:32
9	surprised -- no, I did not. And I doubt if there	15:32
10	is anyone in the universe who has identified	15:32
11	"lipofuscin accumulation" in their keywords and	15:32
12	search terms. It's a very narrow term.	15:32
13	BY MR. FELDSTEIN:	15:32
14	Q. You say, "Years of practice: 24."	15:32
15	Is that out of date, or is it counted	15:33
16	differently from what you told me earlier?	15:33
17	A. It's out of date, and I should update it.	15:33
18	Q. And the "Number of Times Deposed/Testified	15:33
19	in the Last 4 Years" says "26."	15:33
20	Is that accurate?	15:33
21	A. It's probably close. Obviously, it's a	15:33
22	rolling four-year window, and it's going to be a	15:33
23	different precise number as of today, but it's	15:33
24	probably close.	15:33
25	Q. Do you know roughly how many times you've	15:33

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1	ever been deposed or testified as an expert	15:33
2	witness?	15:33
3	A. I've been deposed approximately 70 times,	15:33
4	and I've testified at trial or hearing or	15:33
5	arbitration, I believe, 9 times.	15:33
6	Q. So 79 times being deposed or testifying;	15:33
7	correct?	15:33
8	A. Approximately.	15:33
9	Q. And that's almost four times more than the	15:33
10	number of scientific publications you've published	15:33
11	in 40 years; is that correct?	15:33
12	MR. MILLS: Objection. Form.	15:33
13	THE WITNESS: That ratio is approximately	15:33
14	correct.	15:34
15	BY MR. FELDSTEIN:	15:34
16	Q. Roughly what percent of your income comes	15:34
17	from being a testifying expert, Doctor?	15:34
18	MR. MILLS: Object to form.	15:34
19	Caution to the extent the question calls	15:34
20	for speculation.	15:34
21	THE WITNESS: Well, you say "testifying	15:34
22	expert." Most of my -- the majority of the income	15:34
23	on medical-legal matters is not from testimony.	15:34
24	It's from other things, like reviewing documents	15:34
25	and writing reports and such. So --	15:34

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1	BY MR. FELDSTEIN:	15:34
2	Q. Let me fix the question, then.	15:34
3	MR. MILLS: Sorry, Counsel. You cannot	15:34
4	interrupt the witness.	15:34
5	MR. FELDSTEIN: That's fine. He can keep	15:34
6	going. I'll ask next. I apologize for	15:34
7	interrupting. I was just trying to be efficient.	15:34
8	BY MR. FELDSTEIN:	15:34
9	Q. But go ahead.	15:34
10	A. I think I was done.	15:34
11	MR. FELDSTEIN: Then why did I get yelled	15:34
12	at?	15:34
13	BY MR. FELDSTEIN:	15:34
14	Q. Doctor, let me try to fix the question in	15:34
15	view of what you said.	15:34
16	Roughly what fraction of your income	15:34
17	annually is from serving as an expert witness or	15:35
18	consultant?	15:35
19	MR. MILLS: Objection to form.	15:35
20	THE WITNESS: Because of the nature of my	15:35
21	practice and where I practice and the nature of	15:35
22	the types of patients that I serve, even though	15:35
23	most of my time is spent on medical practice, most	15:35
24	of my income comes from medical-legal.	15:35
25	And the portion varies from year to year,	15:35

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1	but this year, I would expect -- I would estimate	15:35
2	about three-quarters of my income will come from	15:35
3	medical-legal work.	15:35
4	BY MR. FELDSTEIN:	15:35
5	Q. And when you say "medical-legal work,"	15:35
6	you're talking about consulting as an expert in	15:35
7	legal cases; correct?	15:35
8	A. Generally speaking, yes.	15:35
9	MR. FELDSTEIN: Can we take a ten-minute	15:35
10	break?	15:35
11	MR. MILLS: Yes.	15:35
12	(Recess taken.)	15:37
13	MR. FELDSTEIN: Patent Owner -- no further	15:50
14	questions from Patent Owner. Thank you.	15:51
15	MR. MILLS: Thank you.	15:51
16	The deposition is over. The witness	15:51
17	reserves the right to read and review the	15:51
18	transcript.	15:51
19	(Whereupon, the deposition was	
20	concluded at 3:51 p.m.)	
21		
22		
23		
24		
25		

1 STATE OF CALIFORNIA

2
3 REPORTER'S CERTIFICATE

4
5 I, EARLY LANGLEY, a Shorthand Reporter,
6 State of California, do hereby certify:

7 That ANDREW CALMAN, M.D., PH.D., in the
8 foregoing deposition named, was present and by me
9 sworn as a witness in the above-entitled action at
10 the time and place therein specified;

11 That said deposition was taken before me at
12 said time and place, and was taken down in
13 shorthand by me, a Certified Shorthand Reporter of
14 the State of California, and was thereafter
15 transcribed into typewriting, and that the
16 foregoing transcript constitutes a full, true and
17 correct report of said deposition and of the
18 proceedings that took place;

19 That before completion of the proceedings,
20 review of the transcript was requested.

21 IN WITNESS WHEREOF, I have hereunder
22 subscribed my hand this August 29, 2024.

23 

24 EARLY LANGLEY, CSR NO. 3537
25 State of California

1 JAD A. MILLS

2 Jmills@wsgr.com

3 September 11, 2024

4 GENE CO. PTY LTD. v. The Trustees Of Columbia University

5 8/27/2024, ANDREW CALMAN, M.D., PH.D. (#6839149)

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
15 Calendar-PNW@Veritext.com

16
17 Return completed errata within 30 days from
18 receipt of testimony.

19 If the witness fails to do so within the time
20 allotted, the transcript may be used as if signed.

21
22 Yours,
23 Veritext Legal Solutions
24
25

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1 GENE CO. PTY LTD. v. The Trustees Of Columbia University
2 ANDREW CALMAN, M.D., PH.D. (#6839149)
3 E R R A T A S H E E T
4 PAGE_____ LINE_____ CHANGE_____
5 _____
6 REASON_____
7 PAGE_____ LINE_____ CHANGE_____
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20 _____
21 REASON_____
22 _____
23 _____
24 ANDREW CALMAN, M.D., PH.D. Date
25

1 GENE CO. PTY LTD. v. The Trustees Of Columbia University
2 ANDREW CALMAN, M.D., PH.D.(#6839149)

3 ACKNOWLEDGEMENT OF DEPONENT

4 I, ANDREW CALMAN, M.D., PH.D., 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 ANDREW CALMAN, M.D., PH.D.

_____ Date

13 *If notary is required

14 SUBSCRIBED AND SWORN TO BEFORE ME THIS

15 _____ DAY OF _____, 20____.

16
17
18 _____
19 NOTARY PUBLIC

&	1005 2:19 8:23	1029 2:23 9:8	64:7 78:18
& 5:6,17 6:4 148:9 152:4	143:12	10:4 118:16,20	1048 3:20
0	1006 3:25	119:5	56:22 68:25
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00313 7:11,18	137:13,24	119:19,25	1053 3:22
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1	142:7	10:12	1055 3:6 9:11
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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.

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