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Paper 55
Date: May 28, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FOUNDATION MEDICINE, INC.,
Petitioner,

v.

CARIS MPI, INC.,
Patent Owner.

IPR2019-00164
Patent 8,880,350 B2

Before CHRISTOPHER G. PAULRAJ, KRISTI L. R. SAWERT, and DAVID COTTA, *Administrative Patent Judges.*

SAWERT, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–14 ("the challenged claims") of U.S. Patent No. 8,880,350 B2 ("the '350 patent," Ex. 1001). We have jurisdiction under 35 U.S.C. § 6, and enter this Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons set forth below, we determine that Petitioner has shown, by a preponderance of the evidence, that the challenged claims are unpatentable. *See* 35 U.S.C. § 316(e) (2012).

A. Procedural History

Foundation Medicine, Inc., ("Petitioner") filed a Petition for an *inter partes* review under 35 U.S.C. § 311. Paper 3 ("Pet."). Petitioner supported its Petition with the Declaration of Paul T. Spellman, Ph.D. Ex. 1002. Caris MPI, Inc. ("Patent Owner") filed a Preliminary Response. Paper 7. On our authorization (Paper 8), Petitioner filed a Reply to Patent Owner's Preliminary Response (Paper 9) and Patent Owner filed a Sur-Reply to Petitioner's Reply (Paper 10).

On May 30, 2019, pursuant to 35 U.S.C. § 314(a), we instituted trial to determine whether any challenged claim of the '350 patent is unpatentable based on the grounds raised in the Petition:

Claims Challenged	35 U.S.C. §	Reference(s)/Basis
1–14	103(a)[1]	Lu,[2] Illumina[3]
2, 3	103(a)	Lu, Illumina, Muraca[4]
7, 11, 12	103(a)	Lu, Illumina, McDoniels-Silvers[5]

Paper 12, 7–8, 31 ("Institution Decision" or "Inst. Dec.").

Patent Owner filed a Response. Paper 32 ("PO Resp."). Patent Owner supported its Response with the Declaration of Joyce O'Shaughnessy, M.D. Ex. 2021. Petitioner filed a Reply to Patent Owner's Response. Paper 42 ("Pet. Reply"). Petitioner supported its Reply with a Reply Declaration of Dr. Spellman. Ex. 1120. Patent Owner filed a Sur-Reply. Paper 49 ("PO Sur-Reply").

[1] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. § 103, effective March 16, 2013. Because the challenged claims have an effective filing date before this date, the pre-AIA version of § 103 applies.

[2] Mou-Ying Fu Lu and Rong Yu, WO 03/017038 A2 (Feb. 27, 2003) ("Lu," Ex. 1004).

[3] Illumina® Gene Expression Profiling, Technical Bulletin, RNA Profiling with the DASL® Assay (2005) ("Illumina," Ex. 1005).

[4] Patrick J. Muraca, U.S. Patent Application Publication No. 2002/0150966 A1 (Oct. 17, 2002) ("Muraca," Ex. 1006).

[5] Amy L. McDoniels-Silvers et al., Differential Expression of Critical Cellular Genes in Human Lung Adenocarcinomas and Squamous Cell Carcinomas in Comparison to Normal Lung Tissues, 4(2) NEOPLASIA 141–50 (2002) ("McDoniels-Silvers," Ex. 1007).

An oral hearing was held on March 6, 2020. A transcript of the hearing is included in the record. Paper 53 ("Tr.").

B. Real Parties in Interest

Petitioner identifies Foundation Medicine, Inc. and Roche Holdings, Inc., Roche Finance Ltd., and Roche Holding Ltd. as real parties-in-interest. Pet. 2. Patent Owner identifies Caris MPI, Inc., Caris Molecular Diagnostics, and Caris Life Sciences, Ltd. as real parties-in-interest. Paper 4, 2.

C. Related Matters

The '350 patent is the subject of a co-pending litigation in the United States District Court for the District of Massachusetts captioned Civil Action No: 1:17-cv-12194-MLW. Pet. 2; Paper 4, 2. According to Petitioner, that case remains pending, but is currently stayed. Paper 22, 2.

The following Board proceedings also involve the same parties: IPR2019-00165 (U.S. Patent No. 9,092,392 B2), IPR2019-00166 (U.S. Patent No. 9,292,660 B2), IPR2019-00170 (U.S. Patent No. 9,372,193 B2), IPR2019-00171 (U.S. Patent No. 9,383,365 B2), and IPR2019-00203 (U.S. Patent No. 9,292,660 B2). Final Written Decisions in IPR2019-00166 and IPR2019-00203 issued on May 13, 2020. *See* IPR2019-00166 (Paper 53); IPR2019-00203 (Paper 53). Final Written Decisions in IPR2019-00170 and IPR2019-00171 issued on this day. *See* IPR2019-00170 (Paper 56); IPR2019-00171 (Paper 57). Institution of an *inter partes* review in IPR2019-00165 was denied. IPR2019-00165, Paper 7.

D. Summary of the '350 Patent

The '350 patent, titled "System and Method for Determining Individualized Medical Intervention for a Disease State," issued on November 4, 2014. Ex. 1001, (54), (45). The '350 patent relates to a

"system and method for determining individualized medical intervention for a particular disease state," such as cancer, that "includes the molecular profiling of a biological sample from the patient." *Id.* at Abstract.

According to the '350 patent, "[a]lthough the molecular mechanisms behind various disease states have been the subject of studies for years, the specific application of a diseased individual's molecular profile in determining treatment regimens and therapies for that individual has been disease specific and not widely pursued." *Id.* at 1:42–46. The '350 patent further states that "[s]ome treatment regimens have been determined using molecular profiling *in combination with* clinical characterization of a patient such as observations made by a physician . . . , laboratory test results, x-rays, biopsy results, statements made by the patient, and any other medical information typically relied upon by a physician to make a diagnosis in a specific disease." *Id.* at 1:47–55 (emphasis added). The '350 patent states that this combination approach "presents a risk that an effective treatment regimen may be overlooked for a particular individual" because some treatment regimens traditionally administered for one particular disease state also may be effective in treating a different disease state. *Id.* at 1:55–62.

Thus, the '350 patent states, "there is a need for a system and method for determining an individualized medical intervention" for a patient that can identify "additional targets" or "molecular mechanisms, genes, gene expressed proteins and/or combinations of such." *Id.* at 2:18–23, 28–29. The '350 patent states that this approach would provide patients "with a viable therapeutic alternative to those treatment regimens which currently exist." *Id.* at 2:24–27. Figure 2 of the '350 patent, reproduced below, provides an overview of "an exemplary embodiment of a method for determining individualized medical intervention for a particular disease state

that utilizes molecular profiling of a patient's biological specimen that is non disease specific." *Id.* at 5:1–4, 13:7–12.

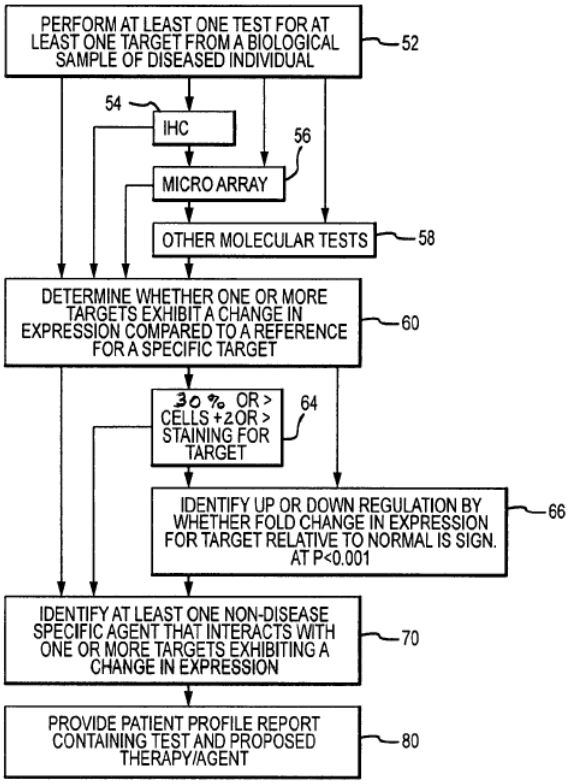


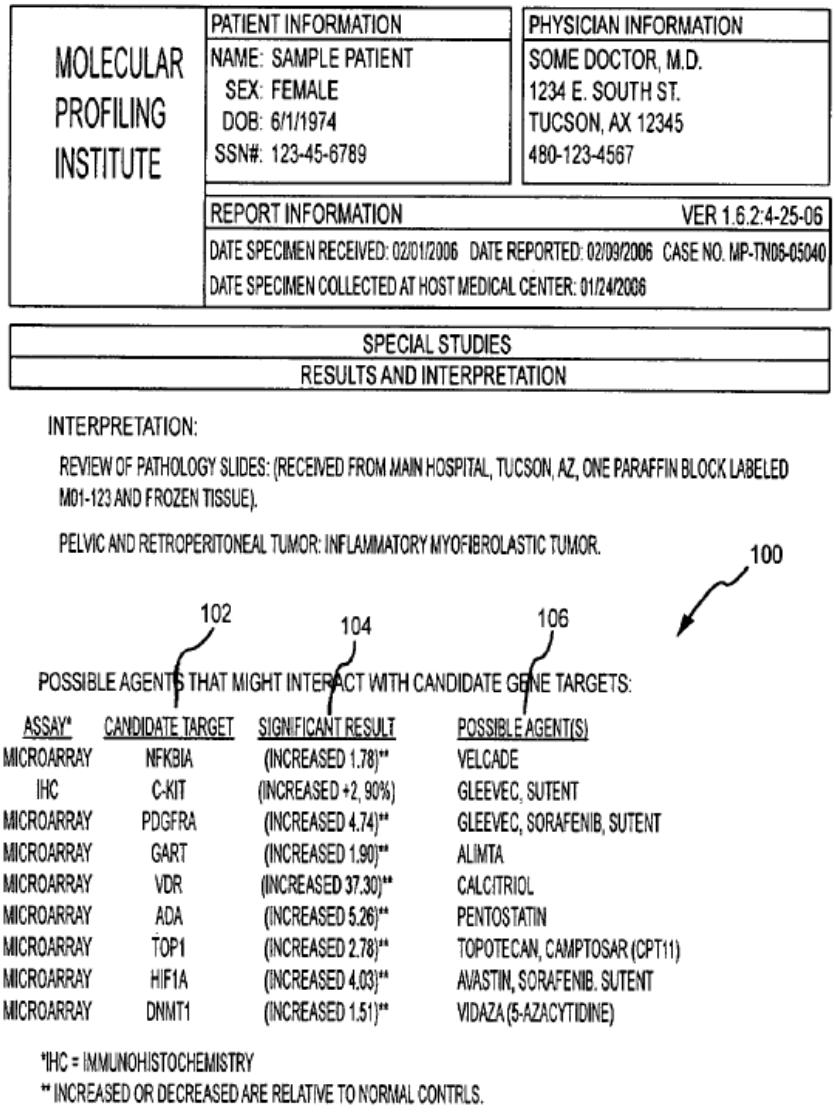
Figure 2 provides an overview of a method for determining an individualized medical intervention that utilizes a patient's molecular profile. *Id.*

In step 52 of Figure 2, at least one test is performed for at least one molecular target (e.g., one or more genes, proteins, and/or molecular mechanisms) from a patient's biological sample. *Id.* at 13:15–21. Tests that may be performed include immunohistochemistry (IHC) analysis 54, microarray analysis 56, and/or any other known molecular tests 58. *Id.* at 13:21–31. The '350 patent states that IHC analysis may be performed for such proteins as c-kit, EGFR, MLH1, and PDGFR. *Id.* at 2:64–3:2. Microarray analysis may be performed for such genes as ESR1, PDGFRA, PTEN, and TOP1. *Id.* at 3:3–20.

In step 60, "a determination is made as to whether one or more of the targets that were tested for in step 52 exhibit a change in expression compared to a normal reference for that particular target." *Id.* at 13:40–43. A change in expression may be observed via differential staining 64, the amount of overexpression or underexpression 66, and/or "by an absence of one or more genes, gene expressed proteins, molecular mechanisms, or other molecular findings." *Id.* at 13:43–63.

Next, "at least one non-disease specific agent is identified that interacts with each target having a changed expression in step 70." *Id.* at 13:64–67. The '350 patent states that a "non-disease specific agent" "is a therapeutic drug or compound not previously associated with treating the patients diagnosed disease that is capable of interacting with the target from the patient's biological sample that has exhibited a change in expression." *Id.* at 14:1–5.

Finally, in step 80, "a patient profile report may be provided which includes the patient's test results for various targets and any proposed therapies based on those results." *Id.* at 14:21–24. Figures 3A through 3D of the '350 patent illustrate an "exemplary patient profile report in accordance with step 80" of Figure 2. *Id.* at 5:5–6. Figure 3A is reproduced below.



MOLECULAR PROFILING INSTITUTE

PATIENT INFORMATION
NAME: SAMPLE PATIENT
SEX: FEMALE
DOB: 6/1/1974
SSN#: 123-45-6789

PHYSICIAN INFORMATION
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480-123-4567

REPORT INFORMATION VER 1.6.2:4-25-06
DATE SPECIMEN RECEIVED: 02/01/2006 DATE REPORTED: 02/09/2006 CASE NO. MP-TN06-05040
DATE SPECIMEN COLLECTED AT HOST MEDICAL CENTER: 01/24/2006

SPECIAL STUDIES
RESULTS AND INTERPRETATION

INTERPRETATION:

REVIEW OF PATHOLOGY SLIDES: (RECEIVED FROM MAIN HOSPITAL, TUCSON, AZ, ONE PARAFFIN BLOCK LABELED M01-123 AND FROZEN TISSUE).

PELVIC AND RETROPERITONEAL TUMOR: INFLAMMATORY MYOFIBROLASTIC TUMOR.

100

102 104 106

POSSIBLE AGENTS THAT MIGHT INTERACT WITH CANDIDATE GENE TARGETS:

ASSAY*	CANDIDATE TARGET	SIGNIFICANT RESULT	POSSIBLE AGENT(S)
MICROARRAY	NFKBIA	(INCREASED 1.78)**	VELCADE
IHC	C-KIT	(INCREASED +2, 90%)	GLEEVEC, SUTENT
MICROARRAY	PDGFRA	(INCREASED 4.74)**	GLEEVEC, SORAFENIB, SUTENT
MICROARRAY	GART	(INCREASED 1.90)**	ALIMTA
MICROARRAY	VDR	(INCREASED 37.30)**	CALCITRIOL
MICROARRAY	ADA	(INCREASED 5.26)**	PENTOSTATIN
MICROARRAY	TOP1	(INCREASED 2.78)**	TOPOTECAN, CAMPTOSAR (CPT11)
MICROARRAY	HIF1A	(INCREASED 4.03)**	AVASTIN, SORAFENIB, SUTENT
MICROARRAY	DNMT1	(INCREASED 1.51)**	VIDAZA (5-AZACYTIDINE)

*IHC = IMMUNOHISTOCHEMISTRY
** INCREASED OR DECREASED ARE RELATIVE TO NORMAL CONTRLS.

Figure 3A illustrates an exemplary patient profile report 100. *Id.*

The report 100 lists the molecular targets profiled 102, the targets tested that exhibited significant changes in expression 104, and the proposed therapeutic agents for interacting with the targets 106. *Id.* at 14:24–28.

The '350 patent discloses a computerized system for generating the report, which includes, among other things, an application program stored in a memory that is accessible by a processor, internal databases, and external databases. *Id.* at 12:47–55. The internal databases can include information about the patient biological sample, patient test results from molecular

profiling, clinical data, and study protocols. *Id.* at 12:65–13:2. The external databases can include drug libraries, gene libraries, disease libraries, and public databases such as GenBank. *Id.* at 13:2–6. The '350 patent states that the processor comprises instructions for assessing a patient's molecular profile, determining whether at least one molecular target exhibits a change in expression "compared to a normal reference," and accessing a drug therapy database to identify drug therapies. *Id.* at 4:1–21. The '350 patent states that a drug therapy may be identified "from an automated review of an extensive literature base and/or an automated review of data generated from clinical trials." *Id.* at 4:42–46.

E. Illustrative Claim

Of the challenged claims, claim 1 is independent and illustrative of the claimed subject matter. Claim 1 recites:

> 1. A system for generating a report identifying at least one therapeutic agent for an individual with a cancer comprising:
>
> a. at least one device configured to assay a plurality of molecular targets in a biological sample to determine individualized molecular profile test values for the plurality of molecular targets, wherein the molecular targets comprise EGFR, KIT, TOP1, MLH1, PTEN, PDGFRA and ESR1; and
>
> b. at least one computer database comprising:
> i. a reference value for the plurality of molecular targets; and
> ii. a listing of available therapeutic agents for said plurality of molecular targets;
>
> c. a computer-readable program code comprising instructions to input the individualized molecular profile test values and to compare said test values with a corresponding reference value in (b)(i);

d. a computer-readable program code comprising instructions to access the at least one computer database and to identify at least one therapeutic agent from the listing of available therapeutic agents for the plurality of molecular targets wherein said comparison to said reference in (c) indicates a likely benefit of the at least one therapeutic agent; and

e. a computer-readable program code comprising instructions to generate a report that comprises a listing of the molecular targets wherein said comparison to said reference indicated a likely benefit of the at least one therapeutic agent in (d) along with the at least one therapeutic agent identified in (d).

Ex. 1001, 16:64–17:27.

II. ANALYSIS

We have reviewed the parties' respective briefs as well as the relevant evidence discussed in those papers. For the reasons discussed in detail below, we determine that Petitioner has shown by a preponderance of the evidence that claims 1–14 of the '350 patent are unpatentable under 35 U.S.C. § 103 as having been obvious.

A. Principles of Law

To prevail in its challenges to the patentability of all claims of the '945 patent, Petitioner must demonstrate by a preponderance of the evidence that the claims are unpatentable. 35 U.S.C. § 316(e) (2012); 37 C.F.R. § 42.1(d) (2018). "In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid. Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016); *see also* 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim"). That burden of persuasion

never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015); *see also In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375–78 (Fed. Cir. 2016) (discussing the burden of proof in *inter partes* review).

A claim is unpatentable for obviousness if, to one of ordinary skill in the pertinent art, "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made." 35 U.S.C. § 103(a) (2006); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including the scope and content of the prior art, any differences between the claimed subject matter and the prior art, the level of ordinary skill in the art, and objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). A petitioner cannot satisfy its burden of proving obviousness by employing "mere conclusory statements." *Magnum Oil*, 829 F.3d at 1380. Moreover, a decision on the ground of obviousness must include "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 550 U.S. at 418 (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

We analyze Petitioner's asserted grounds of unpatentability in accordance with the above-stated principles.

B. Level of Ordinary Skill in the Art

We consider the asserted grounds of unpatentability in view of the understanding of a person of ordinary skill in the art, and thus begin with the level of ordinary skill in the art. The level of ordinary skill in the art is "a prism or lens through which . . . the Board views the prior art and claimed

invention" to prevent hindsight bias. *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

The parties dispute the level of ordinary skill in the art. Relying on the declaration testimony of its declarant, Dr. Spellman, Petitioner contends that as of May 18, 2006—the earliest filing date in the priority chain for the '350 patent—a person of ordinary skill in the art "would have had a Ph.D. in genetics, molecular biology, bioinformatics, or a related field, and at least five years of research experience in an academic or industry setting, including at least two to three years of research experience in the field of cancer genomics." Pet. 16 (citing Ex. 1002 ¶ 32). In our Institution Decision, we preliminarily adopted this level of ordinary skill, which Patent Owner did not dispute in its Preliminary Response. Inst. Dec. 8–9. We also determined that the prior art itself was sufficient to demonstrate the level of ordinary skill in the art at the time of the invention. *Id.*

In response, Patent Owner disputes the type of experience Petitioner proposes for the level of ordinary skill in the art. *See* PO Resp. 4–8; PO Sur-Reply 4–8. Relying on the declaration testimony of its declarant, Dr. O'Shaughnessy, Patent Owner argues that the ordinarily skilled artisan "is an oncologist having a medical degree, at least 10 years of experience treating cancer patients at a medical research facility or hospital, and experience with clinical trials involving anti-cancer therapeutic agents." PO Resp. 4 (citing Ex. 2021 ¶ 14). Patent Owner argues that the '350 patent "details treatment selection and the molecular profiling of cancer patients for treatment recommendations." *Id.* at 4–5 (citing Ex. 1001, 12:44–14:57). Thus, Patent Owner argues, the ordinarily skilled artisan is "an oncologist because oncologists are the people who treat cancer patients and therefore

need to understand which anti-cancer therapies are more or less likely to be of therapeutic benefit to their patients." *Id.* at 5 (citing Ex. 2021 ¶ 14).

Patent Owner argues that Petitioner's definition of an ordinarily skilled artisan is incorrect because Ph.D. researchers "do not treat or select therapy options for cancer patients, and their research findings are not allowed to contribute to the medical record or form the basis for clinical decision-making." *Id.* at 5 (citing Ex. 2020, 126:5–127:8). Instead, a researcher "studies the molecular bases of various cancers to develop new molecular assays to inform, for example, the development of new drugs." *Id.* at 5–6 (citing Ex. 1002 ¶¶ 6, 14). But, Patent Owner argues, "[t]he development of new molecular assays is not the field of the claimed invention," and therefore, "a researcher focused on developing molecular assays cannot be a [person of ordinary skill in the art]." *Id.* at 6.

Patent Owner also argues that the nature of the problem to be solved by the claimed invention supports its definition of an ordinarily skilled artisan. PO Sur-Reply 4–8. Specifically, Patent Owner argues that the prior-art problem "was how to identify treatment options for cancer patients," and "[w]hile the solution entailed the *use* of molecular testing methods," those methods are merely tools used to implement "the idea of using data from assays to identify treatment options independent of cancer lineage." *Id.* at 4–5 (citing Ex. 1118, 99:6–22, 100:2–101:2, 101:13–20).

Based on our consideration of the full record, we maintain our determination that a person with a Ph.D. in genetics, molecular biology, bioinformatics, or a related field, and at least five years of research experience in an academic or industry setting, including at least two to three years of research experience in the field of cancer genomics, would satisfy the definition of an ordinarily skilled artisan in this proceeding. We further

find that, although the ordinarily skilled artisan may have a medical degree instead of, or in addition to, a Ph.D., that artisan need not be a practicing oncologist with experience treating cancer patients.

In determining the level of ordinary skill, various factors may be considered, including "(1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007). These factors are "merely a guide," and the weight or significance ascribed to each depends on the particular case. *Id.* In this particular case, we find that the factors, overall, support Petitioner's definition of an ordinarily skilled artisan.

The "problem" identified in the '350 patent is selecting treatment based on "clinical based criteria," i.e., "the determination that the patient has been diagnosed with a particular disease" via "classical diagnostic assays." Ex. 1001, 1:36–41. The '350 patent purports to solve that problem by utilizing "molecular profiling," i.e., by generating a "diseased individual's molecular profile" and using that profile, instead of "clinical characterizations (such as the diagnosis of a particular type of cancer)[,] to determine a treatment regimen or therapy." *Id.* at 1:42–58. The '350 patent further criticizes using "molecular profiling *in combination with* clinical characterization of a patient such as observations made by a physician," because the use of "medical information typically relied upon by a physician to make a diagnosis in a specific disease" "presents a risk that an effective treatment regimen may be overlooked for a particular individual." *Id.* at 1:47–60 (emphasis added). According to the '350 patent, molecular

profiling can identify "additional targets" or "molecular mechanisms, genes, gene expressed proteins and/or combinations of such," to provide patients "with a viable therapeutic alternative to those treatment regimens which currently exist." *Id.* at 2:18–29.

In addition, claim 1 is directed to a computerized *system* for generating a report identifying at least one therapeutic agent for an individual with a cancer comprising "at least one device configured to assay a plurality of molecular targets." *Id.* at 16:64–17:27. The detailed description of the '350 patent focuses on "various system components," "various databases" (including molecular profiling databases), and communications and displays for generating the report for an end user. *See id.* at 5:20–11:21. The claim language also recites "at least one device configured to assay a plurality of molecular targets," "at least one computer database," and "computer-readable program code" comprising instructions to perform various functions of the computerized system. *Id.* at 17:5–27.

We are not persuaded by Patent Owner's arguments that an ordinarily skilled artisan would necessarily be an oncologist who treats patients. As noted above, the '350 patent teaches away from treatment decisions made from "classical diagnostic assays" and "clinical characterization of a patient such as observations made by a physician." Ex. 1001, 1:36–62. And, although Patent Owner argues that the only "[o]ncologists are the persons qualified to make recommendations for treatments," PO Sur-Reply 5, the '350 patent teaches instead the "the step of identifying a drug therapy" comes "from an *automated review* of an extensive literature base and/or an *automated review* of data generated from clinical trial," Ex. 1001, 4:42–46 (emphases added). We are persuaded by Dr. Spellman's testimony, as supported by record evidence, that it was "researchers in [his] field" that

"were working to associate molecular profiles to potential cancer therapies." Ex. 1120 ¶ 11; *see also* Ex. 1036, 2236 (prior-art database disclosing "120 targets covering 72 disease conditions together with 120 sets of drugs directed at each of these targets"), Ex. 1037, 412 (prior-art "therapeutic target database"). In this regard, although the claimed system could be used by an oncologist as an end-user to help guide treatment decisions, development of the claimed system requires knowledge of "molecular mechanisms, genes, gene expressed proteins and/or combinations of such," Ex. 1001, 2:19–21, that was typically performed by Ph.D. researchers, *see* Ex. 1120 ¶ 11. Thus, we find that the experience and education level of an oncologist would be less relevant for assessing patentability issues for the '350 patent than a Ph.D. researcher with several years' experience in the field of cancer genomics.

Moreover, the claimed system also requires knowledge of computer systems and databases. *See id.* at 5:20–11:21. The type of experience Patent Owner argues is necessary in this case—i.e., experience in treating patients—bears little relevance to computerized systems and databases. *See, e.g.*, Ex. 1119, 398:13–20 (Dr. O'Shaughnessy's testimony that she is not "qualified to make comments about" prior-art reference Lu's "computerized decision support system and databases" in the context of a question of "cancer lineage independence").

Finally, with respect to the educational level of the inventors and the ordinarily skilled artisan, we note that the educational levels and years of experience for both parties' proposed definitions (a Ph.D. and a M.D.) are high. Generally, "[a] less sophisticated level of skill generally favors a determination of nonobviousness, and thus the patentee, while a higher level of skill favors the reverse." *Innovention Toys, LLC v. MGA Entm't, Inc.*,

637 F.3d 1314, 1323 (Fed. Cir. 2011). Thus, although we agree with and have adopted Petitioner's definition for an ordinarily skilled artisan in this proceeding, our analysis and conclusions herein would not change even under Patent Owner's definition. We have considered the qualifications of Dr. Spellman and Dr. O'Shaughnessy, and find that both are qualified to provide opinions about the '350 patent from the perspective of an ordinarily skilled artisan. *See* Ex. 1002, Exhibit A (Dr. Spellman's *curriculum vitae*); Ex. 2021, Exhibit A (Dr. O'Shaughnessy's *curriculum vitae*).

C. Claim Construction

Having defined the ordinarily skilled artisan, we now turn to claim construction. For petitions filed before November 13, 2018[6]—as here—the Board interprets claims in an unexpired patent using the "broadest reasonable construction in light of the specification of the patent." 37 C.F.R. § 42.100(b) (2018); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning that the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). We need not explicitly interpret every claim term for which the parties propose a construction. *See* 35 U.S.C. § 314(a) (2012); *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("[O]nly those terms need be construed that are in controversy, and only to the extent

[6] *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018) (amending 37 C.F.R. § 42.100(b) effective November 13, 2018 to require a federal district court claim construction approach) (now codified at 37 C.F.R. § 42.100(b) (2019)).

necessary to resolve the controversy."); *see also Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (applying *Vivid Techs.* in the context of an *inter partes* review).

At the close of trial, the only claim-construction dispute remaining in this proceeding is whether the claims require, as Patent Owner argues, a system that is "cancer-lineage independent." PO Resp. 24–25. Briefly, Patent Owner argues that a "cancer-lineage independent" system is one that "identif[ies] treatment options for a cancer patient independent of cancer type, based on groups of molecular targets not traditionally or conventionally associated with the patient's specific cancer type." *Id.* at 1. Patent Owner argues that the claims do *not* encompass a "cancer-lineage dependent" system, which, according to Patent Owner, "compares the genetic profile of a patient's tumor with various genes and mutations associated with the *same* type of cancer, and then selects drugs from a database of drugs *known to treat that particular type of cancer*." *Id.* at 2. Petitioner contends that "Patent Owner's construction reads in 'cancer-lineage independence,'" and that "the claims *are not* limited to a system for identifying a cancer lineage-independent therapeutic agent." Reply 6.

1. Overview of Patent Owner's Arguments

Patent Owner argues that cancer-lineage independence is required by the preamble as well as sections (a) and (b) of claim 1. PO Resp. 27–36; *see also* PO Sur-Reply 9–20. As to the preamble, Patent Owner argues that an ordinarily skilled artisan would have understood "a cancer" to mean "any type of cancer." PO Resp. 27–28. As to section (a), Patent Owner argues that an ordinarily skilled artisan would have understood that the group of molecular targets identified in that section (i.e., EGFR, KIT, TOP1, MLH1, PTEN, PDGFRA, and ESR1) "is a pan-cancer or lineage-independent group

of molecular targets." *Id.* at 28–29. Turning to section (b), Patent Owner argues that section (b)(i) requires a database to store a reference value for the "plurality of molecular targets" listed in section (a), while section (b)(ii) requires the database to store "a listing of available therapeutic agents" for the plurality of molecular targets. Patent Owner argues that "[t]he 'available therapeutic agents' are not limited to agents for the patient's specific type of cancer, so the database of section (b) is therefore also cancer lineage independent." *Id.* at 29.

Patent Owner also argues that section (c) and (d) of claim 1 reaffirm the cancer lineage-independence requirements of sections (a) and (b). *Id.* at 29–31. Specifically, Patent Owner argues that section (c)'s "claimed comparison" of the patient's test values with reference values in section (b)(i) "is not based on the lineage of the patient's cancer." *Id.* at 29. And, as to section (d), Patent Owner argues that "[i]t is undisputed that in 2006, at least one therapeutic agent with potential efficacy was associated with each of the molecular targets listed in section (a)." *Id.* at 31. "As a result," Patent Owner argues, "sections (c) and (d) must compare *each* of the listed molecular targets against reference values and be capable of identifying *all* available therapeutic agents for those molecular targets *independent of cancer lineage*." *Id.* at 31.

2. Overview of Petitioner's Arguments

Petitioner disputes Patent Owner's position. *See* Reply 6–12. In particular, Petitioner contends that Patent Owner's reading of claim 1 "imports a narrowing limitation from the specification without any basis in the claims or intrinsic evidence." *Id.* at 6. Petitioner contends that the claim language does not require lineage independence, and that Patent Owner has identified "no explicit lineage-independence term in the claims." *Id.* at 6–7.

As to sections (a) and (b) of claim 1, Petitioner contends that "those limitations are unambiguous and do not justify Patent Owner's construction." *Id.* at 7. Petitioner also contends that Patent Owner's construction conflicts with the prosecution history of the '350 patent family, *id.* at 8–9, and that "importing a lineage-independence limitation would render the claims indefinite," *id.* at 10–12.

3. Analysis

We begin with the words of claim 1 itself. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1301 (Fed. Cir. 2006) ("[C]laim construction must begin with the words of the claims themselves."). As explained above, the parties dispute whether claim 1 *requires* that the system is a "cancer-lineage independent system"—that is, does *not* encompass the allegedly "cancer-lineage dependent" systems of the prior art. For the reasons provided below, we determine that the broadest reasonable interpretation of claim 1 does not require the system to be "cancer-lineage independent."

We see nothing explicit in the plain language of claim 1 that *requires* the claimed system to be a "cancer-lineage independent" system. *See* Ex. 1001, 16:64–17:27. The written description of the '350 patent uses phrases such as "independent of disease lineage diagnosis," *id.* at 2:32–33, 13:12–16, and "not single disease restricted," *id.* at 2:45–47, 13:12–16, to convey the concept of identifying a therapeutic agent independently of cancer lineage. But claim 1 fails to explicitly recite such language relating to cancer lineage. Instead, the plain words of the claim are broadly addressed to a system that determines the molecular profile for an individual with a cancer and generates a report identifying at least one therapeutic

agent[7] based on that individual's molecular profile. *See* Ex. 1001, 16:64–17:27.

Moreover, we note that the plain words of the claim are not directed to a *method* of treating a patient with a cancer-lineage independent approach, as Patent Owner implies. *See* PO Resp. 14 (characterizing the claimed subject matter as setting forth "a paradigm changing approach to treating cancer"). The plain words of the claim are instead directed to a system that generates a report identifying at least one therapeutic agent. *See* Ex. 1001, 16:64–65 (preamble reciting a "system for generating a report identifying at least one therapeutic agent"); *id.* at 17:22–23 (section (e) reciting "comprising instructions to generate a report"). As noted above, Patent Owner distinguishes a "cancer-lineage independent" system from a "cancer-lineage dependent" system, in part, by emphasizing that a "cancer-lineage dependent" system "selects drugs from a database of drugs *known to treat that particular type of cancer*," i.e., an on-label therapeutic agent. PO Resp. 2. But claim 1 does not require that the "at least one therapeutic agent" listed in the report be a "non-disease specific agent" (i.e., an off-label therapeutic agent) as expressly defined in the '350 patent. *See id.* at 14:1–5 (defining "non-disease specific agent" as "a therapeutic drug or compound *not previously associated with treating the patient's diagnosed disease* that is capable of interacting with the target from the patient's biological sample that has exhibited a change in expression" (emphasis added)); *see also* PO

[7] The parties sometimes refer to therapeutic agents as either "on-label," meaning that the therapeutic agent has been indicated for a patient's particular type of cancer, or "off-label," meaning that the therapeutic agent has not been indicated for a patient's particular type of cancer. *See, e.g.*, PO Sur-Reply 2; Reply 8. For clarity, we do the same throughout this Decision.

Sur-Reply 2 (defining "off-label" as "the identified therapy will not be indicated for the patient's cancer"). Moreover, the report itself is agnostic as to whether a physician reading it will apply the concept of cancer-lineage independence to selecting treatments for cancer patients. *See* Ex. 1001, Fig. 3D ("Decisions regarding care and treatment should not be based on a single test such as this test. Rather, decisions on care and treatment should be based on the independent medical judgment of the treating physician taking into consideration all available information . . . .").

Turning to other intrinsic evidence, we are persuaded by Petitioner's contentions that the prosecution histories of related applications undermine Patent Owner's argument that claim 1 requires a cancer-lineage independent system. Reply 8–9. The '350 patent claims direct priority to application No. 11/750,721 ("the '721 application," now U.S. Patent 8,700,335), and provisional application No. 60/747,645 ("the provisional application"). Ex. 1001, codes (63), (60). Claim 12 of the provisional application expressly limited the claimed method to "identifying a drug therapy . . . that is *not single disease restricted*." Ex. 1139, 26 (emphasis added). Original claim 1 of the '721 application (the parent application of the '350 patent) also expressly recited "not single disease restricted." Ex. 1141, 635. This language was amended in a preliminary amendment to "has not been previously associated with treating the diagnosed disease." *Id.* at 531; *see also id.* at 408 (amending claim 1 to recite "wherein the drug therapy has not previously been used to treat the diagnosed disease"). Because the written description of the '350 patent equates disease-lineage independence with

"not single disease restricted,"[8] we find that these claims were explicitly limited to the concept of cancer-lineage independence. *See* Ex. 1001, 13:13–15 (reciting "independent of disease lineage diagnosis (i.e. not single disease restricted)"); *see also* Ex. 1141, 627 (¶ 53) (accord); *Edwards Lifesciences LLC v. Cook Inc.*, 582 F.3d 1322, 1334 (Fed. Cir. 2009) (stating that "i.e." "signals an intent to define the word to which it refers").

Over the course of prosecution of the related applications, however, claims making clear that the invention requires cancer-lineage independence were amended to remove that language, and/or canceled. *See* Ex. 1141, 531 (amending claim 1), 239 (canceling claim 1). For example, claim 21—the claim ultimately issued as claim 1 of the U.S. Patent 8,700,335—originally recited "has not previously been associated with treating the diagnosed disease." *Id.* at 536. But, before allowance, the claim was amended to remove this language and instead recite limitations similar to those found in the '350 patent. *See id.* at 81 (showing final amendments to claim 21).

We find that this prosecution history provides strong evidence that Patent Owner knew how to describe and claim the concept of cancer-lineage

[8] Patent Owner also appears to make a distinction between a "non-disease specific" *system* and a "non-disease specific" *therapeutic agent*, and implies that the prosecution histories are irrelevant because the former is a requirement of claim 1 but the latter is not. PO Resp. 32 n.90; PO Sur-Reply 18–19. To the extent Patent Owner's argument is properly presented, we reject it because Patent Owner itself loosely uses the phrase "cancer-lineage independent" throughout its arguments to modify both the claimed system and the therapeutic agents. *Compare, e.g.*, PO Resp. 2 (referring to a "cancer lineage-*in*dependent approach"), *with id.* at 3 (stating that "the treatment options provided to the oncologist are cancer lineage-independent"). The '350 patent also expressly uses the phrase "that is independent of disease lineage diagnosis" to modify "molecular profiling." Ex. 1001, 13:13–15.

independence, but chose not to—both for the method claims of the '721 application and for the system claims here. *See Microsoft Corp. v. Multi–Tech Sys., Inc.*, 357 F.3d 1340, 1350 (Fed. Cir. 2004) ("Any statement of the patentee in the prosecution of a related application as to the scope of the invention would be relevant to claim construction[.]"); *Biovail Corp. Intern. v. Andrx Pharmaceuticals, Inc.*, 239 F.3d 1297 (Fed. Cir. 2001) (stating that "[c]laim language . . . must be read consistently with the totality of the patent's applicable prosecution history," including prosecution histories of earlier applications). Indeed, Patent Owner could have expressly recited any of above-described terms ("not single disease restricted," "has not been previously associated with treating the diagnosed disease," or "wherein the drug therapy has not previously been used to treat the diagnosed disease") if it intended claim 1 to be limited to a cancer-lineage independent paradigm. But Patent Owner chose not to use such language to describe the claimed invention. For these reasons, we are not persuaded by Patent Owner's argument that "[t]he file histories of the '350 patent and related patents reinforce [its] interpretation of the claims." PO Sur-Reply 15.[9]

[9] Patent Owner also argues that an Interview Summary from the prosecution history of related application 11/750,721 "shows that the applicants and the Examiner understood that the invention related to 'lineage of cancer.'" PO Sur-Reply 13 (citing Ex. 1141, 113). Even so, the Interview Summary does not provide persuasive evidence that the claims here require "cancer-lineage independence." The Interview Summary states that the applicant and the Examiner "[d]iscussed applicant proposed amendment to the claims." Ex. 1141, 113. The Interview Summary also states that, "It was further discussed the recitation of 'lineage of cancer' however no agreement was met." *Id.* Following the interview, Patent Owner did not amend the claims to refer to "lineage of cancer" (whether independent or dependent), or use other words relating to cancer-lineage independence. *See id.* at 81. Thus, if anything, this evidence suggests that

We also disagree with Patent Owner's argument that, even though explicit limitations relating to cancer lineage were removed during prosecution, other language in claim 1 requires a "cancer-lineage independent" system. *See* PO Resp. 27–31 (arguing that the concept of cancer-lineage independence is claimed through the recitation of "a cancer" in the preamble of claim 1, a "plurality of molecular targets" in section (a), a "listing of available therapeutic agents" therefor in section (b), as well as sections (c) and (d)); *see also* PO Sur-Reply 9 (arguing that an ordinarily skilled artisan "reading claim 1 would understand that the preamble and sections (a), (b), (c), and (d) of claim 1 collectively define a system that identifies therapies for a cancer patient independent of cancer lineage").

First, as discussed above, reading "cancer-lineage independence" into the claim would be contrary to the applicant's intent to remove this concept from the claims during prosecution of the '350 patent's parent application. *See Laryngeal Mask Co. v. Ambu*, 618 F.3d 1367, 1373 (Fed. Cir. 2010) (stating that "it would be improper to read" into a claim a limitation removed by amendment, regardless of why eliminated (citing *Kistler Instrumente AG v. United States*, 628 F.2d 1303, 1308 (Ct. Cl. 1980) ("[D]efendant's insist[e]nce upon this court's reading back into the claims limitations which were originally there and were removed during prosecution of the application through the Patent Office cannot be permitted.")")).

Second, we find Patent Owner's attempt to inject the concept of cancer lineage-independence into claim 1 confusing and unhelpful to construing the actual words of that claim. Specifically, Patent Owner's

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applicant did not intend to limit the claims to a cancer-lineage independent system.

claim-construction path requires us to start with words in the preamble ("a disease"), then move on to the listing of molecular targets in section (a) "EGFR, KIT, TOP1, MLH1, PTEN, PDGFRA, and ESR1"), then add to that "a listing of available therapeutic agents" in section (b), and finish with the "comparison" terms in sections (c) and (d) to come to the result that claim 1 *requires* "cancer-lineage independence." *See* PO Resp. 27–31. Although we understand that the claim language must be considered "as a whole," *Pozen Inc. v. Par Pharm., Inc.*, 696 F.3d 1151, 1161 (Fed. Cir. 2012), Patent Owner's arguments fail to add clarity to the plain words of the claim, *see Dayco Prod., Inc. v. Total Containment, Inc.*, 258 F.3d 1317, 1324 (Fed. Cir. 2001) ("If an argument offered in support of a particular claim construction is so convoluted and artificial that it would not be apparent to a skilled artisan reading the patent and the prosecution history, the argument is simply unhelpful to the performance of our [claim-construction] task."). For these reasons, we see no reason to depart from the plain and ordinary meanings of the words used in the claim. *See Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175 F.3d 985, 989–90 (Fed. Cir. 1999) (stating that "there must be a textual reference in the actual language of the claim with which to associate a proffered claim construction").

Nevertheless, as best as we can discern, Patent Owner's claim construction—however stated—focuses on two features of claim 1: (1) the recitation of "a plurality of molecular targets," and (2) the recitation of "a listing of available therapeutic agents for said plurality of molecular targets." Specifically, Patent Owner argues:

> A POSA would understand that the patentee has chosen to *communicate the concept of cancer lineage-independence* through the selection of *molecular targets not specific to any specific type of cancer* and the consideration of *all potential*

> *therapeutic agents* regardless of the origin of the individual patient's cancer.

PO Resp. 32 (emphases added).

As to the molecular targets, it is undisputed that the plurality of molecular targets (i.e., EGFR, KIT, TOP1, MLH1, PTEN, PDGFRA, and ESR1) recited in claim 1 were not associated with one particular type of cancer in the prior art at the time of the '350 patent.[10] Ex. 2021 ¶ 55; Ex. 2020, 96:22–97:12. Even so, that fact does not necessarily result in a "cancer-lineage independent" system, because the remaining sections of claim 1 do not require the identification of *all* available therapeutic agents, including off-label therapeutic agents.

Put differently, the '350 patent characterizes the disclosed system as "identifying a non-specific disease therapy or agent capable of interacting" with the molecular markers, i.e., an off-label therapeutic agent. Ex. 1001, Abstract; *id.* at 14: 1–5 (defining a "non-disease specific agent" as "a therapeutic drug or compound *not previously associated* with treating the patient's diagnosed disease" (emphasis added)).[11] But nothing in the plain language of sections (a)–(e) requires an identification of *all* available

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[10] We contrast Patent Owner's arguments in this case with those in IPR2019-00166, in which Patent Owner argued that a claim directed to "[a] system for generating a report identifying a therapeutic agent for an individual with *lung cancer*" was cancer-lineage independent because an ordinarily skilled artisan would have recognized that the recited molecular targets (i.e., PTEN, CTNNB1, cKIT, BRAF and PIK3CA) are not traditionally associated with *lung cancer*. IPR2019-00166, Paper 29, 31. Here, however, the preamble of claim 1 recites "an individual with a cancer," rather than a specific type of cancer.

[11] Patent Owner agrees that an off-label therapeutic agent is one "not . . . indicated for the patient's cancer." PO Sur-Reply 2.

therapeutic agents, i.e., both on-label and off-label therapeutic agents, for those molecular markers. Instead, the plain language simply requires "a listing of available therapeutic agents." Ex. 1001, 17:8–9. Accordingly, while claim 1 encompasses a system that is capable of identifying both on-label and off-label therapeutic agents, claim 1 does not *require* the identification of off-label therapeutic agents, and thus is not restricted to a "cancer-lineage independent" approach.

And Patent Owner's requirement—that the system be capable of identifying *all* available therapeutic agents—cannot be read into the claim from the written description, because the '350 patent itself does not disclose all the therapeutic agents there were available for certain molecular targets as of May 18, 2006. Specifically, Table 1 of the '350 patent purports to present only "[s]ome of the non-disease specific agents that have been found to interact with specific targets" such as EGFR (i.e., Erbitux™ and Rapamycin™). Ex. 1001, 14:5–20. Moreover, it was known in the art, as Dr. Spellman explains, that as of the earliest priority date of the '350 patent, other EGFR inhibitors were known, i.e., gefitinib (Iressa®) and erlotinib (Tarceva®). Ex. 1002 ¶ 44 (citing Ex. 1009, 294; Ex. 1059, 107).

Finally, we agree with Petitioner that adding a "cancer lineage-independence" requirement to claim 1 would result in some ambiguity, given that the association of a particular molecular target with a particular cancer changes over time. Reply 10–11. For example—and as Petitioner points out—Dr. O'Shaughnessy provided inconsistent answers to questions about whether certain assays directed to the claimed molecular targets would be "lineage independent" or "lineage dependent." *Compare* Ex. 1119, 315:19–21 (testifying that "the only proven clinical utility of an EGFR inhibitor was in lung cancer" in 2006), *with id.* at 338:18–339:1 (testifying

that it was not standard to check lung cancer for EGFR mutation in 2006); *compare id.* at 317:16–18 (testifying that TOP1 is associated with colorectal cancer), *with id.* at 318:12–14 (testifying that TOP1 "was definitely not proven as a biomarker for colorectal cancer"). To add further confusion, when asked whether the '350 patent discloses "the lineage-independent concept," Dr. O'Shaughnessy testified during cross examination that "[i]t's a little hard to say 'the lineage-independent concept,' because that's such a broad way of stating it" and "I don't know exactly what you mean by 'the lineage-independent concept.'" *Id.* at 452:2–13. Given these uncertainties, we are disinclined to adopt Patent Owner's argument that the claims require a "cancer-lineage independent" approach.

In sum, we do not construe the claims to *require* the concept of "cancer-lineage independence," as Patent Owner argues. Despite any support that might be otherwise present for such a requirement in the written description, we are not persuaded that the claim language itself supports Patent Owner's construction. In determining the scope of the invention, "the name of the game is the claim." *In re Hiniker Co.*, 150 F.3d 1362, 1369 (Fed. Cir. 1998). And here, consistent with its plain language, claim 1 requires a system for determining the molecular profile for an individual with a cancer that generates a report identifying at least one therapeutic agent indicating a likely benefit, based on that individual's molecular profile. We also determine that the claimed system may identify a cancer-lineage independent (i.e., off-label) therapeutic agent, but is not required to do so.

D. Asserted References

Before turning to Petitioner's asserted grounds of unpatentability, we provide a brief summary of the asserted references.

1. Lu

Lu teaches a "computerized decision support system for selecting the optimum treatment for human cancer." Ex. 1004, (54). The system predicts "which of one or more drugs suitable to treat a cancerous condition in a patient are the optimum drug(s)" "based upon the particular patient's genotype." *Id.* at (57). According to Lu, the system comprises:

> a PCR kit and/or a gene chip designed to detect multiple genes, expressions and/or mutations associated with a particular cancer using a sample of the patient's tissue or blood; a detector for accepting receipt of the gene chip toward analyzing the patient's genotype; a database describing the correlation of patient genotypes and the efficacy and toxicity of various anti-cancer drugs used in treating patients with a particular cancerous condition; and a computerized decision support system operably connected to the detector for correlating the output of the detector to the database.

Id. ¶ 18.

Lu teaches that the detector outputs genetic data into a "bioinformatic software package" that compares the genetic data with "a database of data toward providing the physician with a recommendation into plain English in order to assist doctors to select the most effective medicine with the least amount of side effects for patients." *Id.* ¶ 42. Lu teaches that the software may be "customized for a single disease or multiple diseases." *Id.*

In a preferred embodiment, the system detects the breast cancer genes ER Alpha, Her2, ErbB1, BRAC1, and BRAC2. *Id.* ¶ 22. For example, the system detects upregulation or downregulation of the expression of those genes, or mutations in those genes. *Id.* ¶¶ 51, 53. Depending on the results, the system provides an output that recommends or discourages the use of certain drug(s) for cancer therapy. *Id.* ¶¶ 52, 54.

2. Illumina

Illumina is a technical bulletin prepared by Illumina, Inc. Ex. 1005.[12] Illumina teaches that "[m]icroarray analysis of gene expression has proven to be a remarkable tool," but has faced challenges because of the lack of high-quality and/or poor integrity RNA. *Id.* at 1 (Introduction). Illumina discloses a "gene expression assay for microarrays that is capable of utilizing partially degraded RNA." *Id.*

Specifically, Illumina discloses the "cDNA-mediated Annealing, Selection, extension and Litigation (DASL) Assay," which "can monitor RNA expression of up to 1536 sequence targets." *Id.* According to Illumina, "the DASL Assay offers researchers the opportunity to analyze hundreds to thousands of RNA transcripts derived from previously collected, preserved samples." *Id.*

Illumina discloses a particular DASL assay—the "DASL Cancer Panel"—that "is a pool of selected probe groups that targets 502 genes from ten publicly available gene lists." *Id.* at 4 ("The DASL Cancer Panel"). Illumina teaches that the "[g]enes were chosen based on the frequency of appearance on these lists and the frequency of literature citations of these genes in association with cancer." *Id.* The DASL Cancer Panel includes, among others, the genes EGFR, KIT, TOP1, MLH1, PTEN, PDGFRA, and ESR1. *Id.* at Table 1.

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[12] In its Preliminary Response, Patent Owner argued that Petitioner had failed to establish that Illumina qualifies as a prior-art printed publication. Prelim. Resp. 18–28. We discern, following trial, that Patent Owner no longer pursues this argument. *See generally* PO Resp., PO Sur-Reply. Based on the evidence of record, we determine that Petitioner has met its burden of establishing that Illumina qualifies as a prior art printed publication.

Illumina further teaches that the DASL assay can be used to analyze differential expression profiles, and provides an example comparing the expression of RNA from both normal prostate tissue and a prostate cancer cell line. *Id.* at 5. Illumina states that "expression analysis using degraded RNA will properly reflect biological differences using intact RNA." *Id.* at 6. Illumina also teaches the DASL assay can be used to study differences in expression in clinical samples, to "report[] biologically relevant results." *Id.* at 7 ("Application to Clinical Samples").

Finally, Illumina discloses that the DASL assay provides for high-throughput expression profiling, because it allows for the analysis of 16 or 96 samples simultaneously. *Id.* at 8 ("Summary").

3. Muraca

Muraca discloses a "system for accessing, organizing, and displaying tissue information." Ex. 1006 ¶ 1. The system "correlate[s] molecular profiling data obtained from tissue microarrays with patient information in a specimen-linked database." *Id.* The specimen-linked database "is a repository of information including . . . information relating to phenotype, genotype, pathology, and expression of biomolecules in tissues, and including information relating to the medical history of the individuals who are the sources of tissues being analyzed," such as demographic and epidemiologic information. *Id.* ¶ 9.

Muraca teaches that, in one embodiment, the "system provides information relating to diagnosis, prognosis, or likelihood of recurrence of a disease." *Id.* ¶ 22. Specifically, a user inputs a patient's biological characteristic(s), such as gene or protein expression, into the system, which then "retrieves information from the specimen-linked database about the

disease state associated with the particular expression pattern identified by the user." *Id.*

Muraca also teaches embodiments in which the system identifies drug biological targets for drug therapy and potential drugs, provides information relating to clinical trials, and suggests treatment options for a particular disease diagnosis or prognosis. *Id.* ¶ 23.

4. McDoniels-Silvers

McDoniels-Silvers presents a study of the differential expression of certain genes in human lung adenocarcinomas and squamous cell carcinomas compared to normal lung tissues. Ex. 1007, Abstract. McDoniels-Silvers examined the expression of 588 genes using a human cDNA expression array. *Id.* McDoniels-Silvers obtained tumor tissue samples from cancer patients, and compared the results to normal tissues. *Id.* at 142. McDoniels-Silvers found that 45 of those genes "were differentially expressed by at least two-fold in tumor tissues compared to corresponding normal tissues." *Id.* at 141. McDoniels-Silvers teaches that "[t]hese gene expression changes may directly contribute to the initiation or progression of human lung cancer or may be secondary effects of the tumorigenesis process," but "[r]egardless, many of these differences may be useful in the diagnosis and/or treatment of" lung cancers. *Id.*

E. Obviousness over Lu in View of Illumina

Petitioner contends that claims 1–14 are unpatentable as having been obvious over Lu in view of Illumina. Pet. 23–58. Patent Owner opposes. PO Resp. 48–61; PO Sur-Reply 6–23. Having considered the totality of the arguments and evidence, we find that Petitioner has shown by a preponderance of the evidence that claims 1–14 are unpatentable as having been obvious over Lu in view of Illumina.

1. Limitations of the challenged claims

Petitioner contends that the combination of Lu and Illumina discloses or suggests each element of the challenged claims. Petitioner presents arguments mapping the language of claims 1–14 to the disclosures of each reference. Pet. 23–48. We have reviewed Petitioner's arguments and, for the reasons articulated below, find that a preponderance of the evidence supports Petitioner's contentions.

a) Claim 1

Claim 1 recites, in the preamble, a "system for generating a report identifying at least one therapeutic agent for an individual with a cancer." Ex. 1001, 16:64–65. We agree with Petitioner that Lu teaches this portion of the claim by disclosing:

> It is [one] object of the present invention to identify which drugs are optimum to treat other cancerous conditions in patients. It is another object of the present invention to provide a computerized decision support system to provide in plain language to a physician a recommendation as to the optimum anti-cancer drug to prescribe for a patient.

Ex. 1004 ¶¶ 15–16; *see also* Pet. 23–24 (citing Ex. 1002 ¶ 125). Lu teaches that the "recommendation" may be in the form of a printed-out report, thus teaching "generating a report." *See* Ex. 1004 ¶ 45 ("Report processor 47 provides the computer analysis from the optimization processor 46 in a printout form 49 or on a computer screen 19."); *see also id.* at Fig. 4 (referring to printout form 49 as the "Final Report").

Next, in section (a), claim 1 recites "at least one device configured to assay a plurality of molecular targets in a biological sample to determine individualized molecular profile test values for the plurality of molecular targets, wherein the molecular targets comprise EGFR, KIT, TOP1, MLH1,

PTEN, PDGFRA and ESR1." Ex. 1001, 16:66–17:4. We agree with Petitioner that "Lu and Illumina disclose this limitation in combination." Pet. 24 (citing Ex. 1002 ¶¶ 126–30).

Specifically, Lu "discloses a PCR kit and/or a gene chip designed to detect multiple genes, expressions and/or mutations . . . using a sample of the patient's tissue or blood." Ex. 1004 ¶¶ 18, 19, 22; Pet. 24. Lu discloses that multiple targets can be assayed by, for example, RT-PCR, and that the assays "produce test values" in the form of up-regulation or down-regulation data. Ex. 1004 ¶¶ 34, 35, 51, 52; Ex. 1002 ¶ 126. Lu discloses assaying the genes ESR1 (also known as ER Alpha[13]) and EGFR (also known as ERBB1[14]), but does not disclose the remaining genes recited in claim 1. Ex. 1004 ¶¶ 22, 48, 51, 53, 54; Pet. 18 (citing Ex. 1002, ¶¶ 101–103). Illumina, however, discloses the DASL Cancer Panel, which allows the determination of expression values for up to 1536 nucleic acid sequence targets that correspond to 502 cancer-related genes. Ex. 1005, 1, 3; Pet. 25 (citing Ex. 1002 ¶ 127). Such targets include, as Petitioner points out, the genes EGFR, KIT, TOP1, MLH1, PTEN, PDGFRA and ESR1. Ex. 1005, 4 (Table 1); Pet. 26–27 (citing Ex. 1002 ¶¶ 128–29). Thus, taken together, Lu and Illumina recite the molecular targets recited in claim 1.

Claim 1 recites in section (b) "at least one computer database comprising: i. a reference value for the plurality of molecular targets; and ii. a listing of available therapeutic agents for said plurality of molecular targets." Ex. 1001, 17:5–9. We agree with Petitioner that Lu discloses a computer database with biological profile data that includes reference values

[13] *See* Ex. 1060 (describing "ER Alpha" as a synonym of "ESR1").
[14] *See* Ex. 1044 (describing "ERBB1" as a synonym of "EGFR").

for molecular targets and a listing of available therapeutic agents for the molecular targets. Pet. 28–32. Specifically, Lu discloses a "computerized decision support system" that comprises "a database." Ex. 1004 ¶ 18, Fig. 4 (disclosing "Gene & Drug Database" 42). Lu explains that the gene and drug database stores "criteria and drug information" to which the expression levels of molecular targets are compared to determine, e.g., upregulation or downregulation. *Id.* ¶¶ 18, 50, 51; Pet. 30 (citing Ex. 1002 ¶ 133). Lu also discloses that the gene and drug database is updated "as new drugs are developed and as existing drugs are used more and more." Ex. 1004 ¶¶ 4, 44. Thus, we agree with Petitioner that this disclosure satisfies the claim limitation of "a listing of available therapeutic agents for said plurality of molecular targets." Pet. 31 (citing Ex. 1002 ¶ 136).

We also agree with Petitioner that Illumina discloses comparing test expression values derived from a cancerous sample to reference values from a normal sample. *Id.* at 30–31 (citing Ex. 1002 ¶¶ 134–35). For example, in Figure 4, Illumina provides a comparison of the expression data of normal prostrate cells to LNCaP cells, a prostate cancer cell line. Ex. 1005, 5 (Fig. 4); *see also id.* at 6–7 (Fig. 6 (comparing expression values from prostrate and colon cancer samples to normal tissues)).

Next, claim 1 recites in section (c) "a computer-readable program code comprising instructions to input the individualized molecular profile test values and to compare said test values with a corresponding reference value in (b)(i)." Ex. 1001, 17:10–13. We agree with Petitioner that Lu discloses this limitation. Pet. 32–33 (citing Ex. 1002 ¶ 137). Lu discloses that the database "correlat[es] . . . patient genotypes and the efficacy and toxicity of various anti-cancer drugs . . . with a particular cancerous condition," and that the "computerized decision support system"

"correlat[es] the output of the detector to the database." Ex. 1004 ¶ 18. Specifically, the system "serves to correlate and calculate the raw signals/data provided . . . and will interpret the raw signals/data according to criteria and drug information stored in the system database." *Id.* ¶ 50.

Claim 1 further recites in section (d):

> a computer-readable program code comprising instructions to access the at least one computer database and to identify at least one therapeutic agent from the listing of available therapeutic agents for the plurality of molecular targets wherein said comparison to said reference in (c) indicates a likely benefit of the at least one therapeutic agent.

Ex. 1001, 17:14–21. We agree with Petitioner that Lu teaches this limitation by disclosing:

> a database which associates patient genotypes and the efficacy and toxicity of various anti-cancer drugs used in treating patients with a particular cancerous condition connected to the detector [that] correlates the output of the detector to the database to provide a recommendation as to which drugs are optimum for treating the patient's cancer.

Ex. 1004, Abstract; *see also id.* ¶ 38. Lu also teaches an "optimization processor" that "consists of a number of search algorithms that find the best fit results for the patient using the knowledge contained in the . . . gene and drug databases," and "provides [a] computer analysis" to determine "the optimum drugs based upon a patient genotype." *Id.* ¶¶ 45–46; Pet. 36 (citing Ex. 1002 ¶ 143). The computer analysis may list the benefits of the drug as well as its side effects. Ex. 1004 ¶¶ 45–46.

Finally, claim 1 recites in section (e) "a computer-readable program code comprising instructions to generate a report that comprises a listing of the molecular targets wherein said comparison to said reference indicated a likely benefit of the at least one therapeutic agent in (d) along with the at

least one therapeutic agent identified in (d)." Ex. 1001, 17:22–27. Petitioner asserts that Lu discloses the creation of a patient profile report that includes test results for various targets and proposed therapies. Pet. 37–38 (citing Ex. 1002 ¶¶ 144–145).[15] We agree. Specifically, Lu's system comprises report processor software that "provide[s] the physician with the plain language recommendation as to which drugs to use for a particular patient." Ex. 1004 ¶¶ 44–45. In Figure 4, Lu shows the "recommendation" in the form of a printed-out "final report" 49. *Id.* (Fig. 4). Lu discloses sample listings of raw signals or data generated by the system detector, *id.* ¶¶ 51, 53, and teaches that the "bioinformatic software program correlate[s] and calculate[s]" that data with the genetic and drug database, to result in a "plain spoken language" report, *id.* ¶¶ 50, 52, 54.

We are not persuaded by Patent Owner's arguments that the combination of Lu and Illumina fails to teach the limitations of claim 1. PO Resp. 36–46; PO Sur-Reply 21–25. Patent Owner argues that "even if Lu and Illumina could be combined, the resulting combination would lack a key element of the claims, namely, a system that identifies a therapeutic agent for a cancer patient independent of cancer lineage." PO Resp. 36. But, as explained in detail above, we do not read the claims as *requiring* that the claimed system is "cancer-lineage independent." *Supra* § II.C.3.

[15] Petitioner also asserts that this limitation is not entitled to patentable weight because it is directed to the content of information and lacks a requisite functional relationship (i.e., is non-functional descriptive material). Pet. 37 (citing *Praxair Distribution, Inc. v. Mallinckrodt Hosp., Prods. IP Ltd.*, 890 F.3d 1024, 1032 (Fed. Cir. 2018)). We need not resolve this issue, because for the reasons described above, we are satisfied that Lu teaches this limitation.

Specifically, under our construction, the system of claim 1 may identify a cancer-lineage independent (i.e., off-label) therapeutic agent, but is not required to do so. *Id.* Patent Owner conceded at the oral hearing that, if we construed the claims as encompassing a "lineage dependent analysis," then the prior art taught the claimed subject matter. Tr. 35:15–36:12. Specifically, Patent Owner concedes that Lu teaches the identification of "various anti-cancer drugs used in treating patients with a particular cancerous condition," i.e., on-label therapeutic agents. PO Resp. 37 (quoting Ex. 1004 ¶ 18 (emphasis omitted)).

But even if we read claim 1 as *requiring* a cancer-lineage independent approach (i.e., one in which both the molecular markers are not associated with any one particular cancer *and* the system *must be* capable of identifying off-label therapeutic agents), we still find that the combination of Lu and Illumina discloses or suggests each and every limitation of claim 1.

First, Illumina's microarray of molecular targets is clearly "pan-cancer" and, thus, "cancer-lineage independent," as Patent Owner uses that term in its arguments. Specifically, Illumina discloses the DASL Cancer Panel, which allows for the determination of expression values for up to 1536 nucleic acid sequence targets that correspond to 502 cancer-related genes. Ex. 1005, 1, 3; Pet. 25 (citing Ex. 1002 ¶ 127). Illumina teaches that the panel can detect molecular targets associated with a wide variety of cancers, including at least prostate, colon, and breast cancers. Ex. 1005, 5–8; Ex. 1120 ¶ 65; Reply 20. Illumina's molecular targets include EGFR, KIT, TOP1, MLH1, PTEN, PDGFRA and ESR1—each and every molecular target listed in claim 1. Ex. 1005, 4 (Table 1); Pet. 26–27 (citing Ex. 1002 ¶¶ 128–29); *see also* Ex. 1119, 401:11–403:11 (testimony of Dr. O'Shaughnessy that Illumina's DASL panel includes all the claimed

molecular targets). Thus, as Patent Owner describes its listing of molecular targets as "pan-cancer" and "cancer-lineage independent," so too is Illumina's listing of molecular targets. *See* PO Resp. 28 (arguing that, because "a POSA reading the group of molecular targets identified in section (a) of claim 1 would recognize that it is not directed at any one specific type of cancer," they are a "lineage-independent group").

That Illumina discloses a "cancer-lineage independent" panel of molecular targets is also well supported by the testimony of both Dr. O'Shaughnessy and Dr. Spellman. *See* Ex. 1119, 333:3–20 ("Q. And it's also your opinion that the panel . . . contain[ing] those seven targets [of claim 1] is necessarily lineage independent, correct? A. (Dr. O'Shaughnessy) Yes."); *id.* at 426:16–21 (testimony of Dr. O'Shaughnessy that "there are genes on the Illumina set that come from a wide variety of cancers"); *id.* at 439:1–3 (testimony of Dr. O'Shaughnessy that the DASL assay can analyze many targets in one assay); Ex. 1118, 202:3–22 (testimony of Dr. O'Shaughnessy that "microarrays were built" to "assay a wide variety of genes" simultaneously); Ex. 1120 ¶¶ 64–66 (Dr. Spellman's declaration testimony).

Second, even if the "cancer-lineage independent" system must be capable of identifying off-label therapeutic agents, we find that Lu teaches this requirement, or that, at minimum, the combination of Lu and Illumina suggests this requirement to an ordinarily skilled artisan. Although Patent Owner argues that Lu is limited to identifying therapeutic agents "from a database of drugs known to treat that particular cancer," PO Resp. 39 (emphasis omitted), we find that Lu's disclosure is broader than that.

Specifically, Lu generally teaches that its system can be used "to predict or identify the optimum drug for treating cancers *other th[a]n breast*

cancer," and "can be used to identify an optimum drug for treating *virtually any disease* for which there exists an established correlation between a patient genotype and the efficacy and toxicity of each of a group of drugs developed to treat the general condition." Ex. 1004 ¶ 56 (emphases added). Lu also teaches that the effectiveness of a particular drug can vary "from patient to patient"—even patients within the same patient group. *Id.* ¶ 3. And Lu teaches that "there exists a known database" of therapeutic agents "developed typically through clinical trial," and that "as new drugs are developed and existing drugs are used more and more, the database grows." *Id.* ¶ 4.

We find that these disclosures provide a preponderance of evidence that supports Petitioner's position (and Dr. Spellman's testimony) that Lu's system is capable of determining therapeutic agents based on the individual patient's *genotype*, and therefore is not limited to drugs indicated for that patient's *particular cancer* type (i.e., on-label therapeutic agents). *See* Ex. 1004 ¶ 10 ("Accordingly, it is an object of the present invention to provide a system which can be used by doctors to identify which pharmaceutical drugs from among several potential choices is indeed the most appropriate to treat a patient's particular medical condition."); *id.* ¶ 46 (describing presentation of "recommendations as to the optimum drugs based upon a patient genotype to the doctor in an understandable manner"); *id.* ¶ 47 (describing "diagnostic software program with accompanying database for prediction of gene and drug interaction"); *see also* Ex. 2068, 146:18–147:1 (Dr. Spellman's testimony); Ex. 1120 ¶¶ 55–63.

At a minimum, we find that the combination of Lu and Illumina suggests to an ordinarily skilled artisan a system capable of identifying off-label therapeutic agents. We find credible, and supported with preponderant

record evidence, Dr. Spellman's unrebutted testimony that an ordinarily skilled artisan would have understood molecular profiling to have been a recognized method for identifying therapeutic agents, irrespective of a patient's particular disease, before the May 16, 2006, effective filing date of the '350 patent. Ex. 1002 ¶¶ 35–46.

Specifically, Dr. Spellman provides evidence that, by the early 2000s, "microarrays were widely used in genomics-based research to predict drug response based on gene expression profiles." *Id.* ¶ 64 (citing Ex. 1026, 10787 (stating that DNA microarrays "permit the simultaneous measurement of the expression levels of thousands of genes, rais[ing] the possibility of an unbiased, genomewide approach to the genetic basis of drug response"). Dr. Spellman also provides evidence that "[c]ommercial microarrays with many thousands of genes on a single device were widely available" as of the early 2000s. *Id.* ¶¶ 65–66 (citing Ex. 1027; Ex. 1028). As Dr. Spellman explains, these arrays provided the "ability to screen hundreds to thousands of potential targets in a single experiment." *Id.* ¶ 66.

Dr. Spellman also provides evidence that, before 2006, various databases providing reference values for the expression of molecular targets, as well as databases correlating known drug targets and their respective drugs, were also well known in the art. *Id.* ¶¶ 68–74, 76–80 (describing the ONCOMINE databases (Exs. 1030–32), the ArrayExpress database (Ex. 1033), the Stanford Microarray Database (Ex. 1034), the TRMP ("Therapeutically Relevant Multiple Pathways") database (Ex. 1036), the TTD ("Therapeutic Target Database") (Ex. 1037), and the Cosmic ("Catalog of Somatic Mutations in Cancer") database (Ex. 1038)).

We agree with Dr. Spellman that, given the state of the art, an ordinarily skilled artisan would have understood that the combination of

Illumina's microarray of molecular targets and Lu's database of therapeutic agents would suggest the identification of off-label therapeutic agents. *See* Ex. 1120 ¶¶ 52–54. As noted above, Lu teaches the use of existing databases of therapeutic agents "developed typically through clinical trial," and that "as new drugs are developed and existing drugs are used more and more, the database grows." Ex. 1004 ¶ 4.

Patent Owner argues that Lu's database would be limited to therapeutic agents already known to be useful for treating a patient's particular disease—i.e., on-label drugs. PO Resp. 37. We disagree. The prior-art TRMP, TTD, and Cosmic databases were well-known, commercially-available databases that listed therapeutic agents for a wide variety of molecular targets, regardless of disease type. Ex. 1002 ¶¶ 76–80; Ex. 1036; Ex. 1037; Ex. 1038. It would make little sense for the ordinarily skilled artisan to remove from those databases references to any off-label therapeutic agents for a patient's particular disease, especially given that Patent Owner has conceded that that artisan would have been motivated to replace Lu's microarray with Illumina's DASL assay, as explained below. *See* Tr. 54:14–55:8; *see also infra* § II.E.2.a. We also emphasize that claim 1 is directed to a system for identifying a therapeutic agent; there is no requirement that the identified therapeutic agent be used in a method for treating an individual with cancer.

In sum, we determine that Petitioner has shown, by a preponderance of the evidence, that the combination of Lu and Illumina teaches or suggests each and every limitation of claim 1.

b) Dependent claims 2–14

Having decided that the combination of Lu and Illumina teaches or suggests each and every limitation of claim 1, we turn to the remaining

claims of the '350 patent, which are all directly dependent on claim 1 (i.e., claims 2–14). We find that Petitioner also shows by a preponderance of the evidence that Lu and Illumina account for the limitations in these claims. Pet. 38–48. We have also reviewed Dr. Spellman's testimony and find that a preponderance of the evidence supports his contention that the cited references collectively disclose or suggest each and every limitation of claims 2–14. *See* Ex. 1002 ¶¶ 146–147 (claim 2) (citing Ex. 1004 ¶¶ 4, 23; Ex. 1037, Abstract; Ex. 1055, Abstract, D671); *id.* ¶¶ 148–149 (claim 3) (citing Ex. 1004, Abstract; Ex. 1037, Abstract; Ex. 1055, Abstract, D671); *id.* ¶¶ 150–151 (claim 4) (citing Ex. 1004 ¶ 45, Fig. 4); *id.* ¶¶ 152–153 (claim 5) (citing Ex. 1004 ¶¶ 23, 36, 37, 42–44, 47, 50); *id.* ¶¶ 154–157 (claim 6) (citing Ex. 1004 ¶¶ 18, 38, 42, 50–54; Ex. 1005, 3, 7, Figs. 4, 6, 7); *id.* ¶¶ 158–160 (claim 7) (citing Ex. 1004 ¶¶ 43, 46; Ex. 1056, 667, 668; Ex. 1047, 2386); *id.* ¶¶ 161–163 (claim 8) (citing Ex. 1004, Abstract, ¶¶ 18–20, 31–33, 47, 49, Fig. 2, claims 2 and 7; Ex. 1005, 5–8); *id.* ¶¶ 164–166 (claim 9) (citing Ex. 1004, Abstract, ¶¶ 18, 19, 34, 36, 51, 53; Ex. 1005, 1, 4, 6–8, Fig. 7); *id.* ¶¶ 167–170 (claim 10) (citing Ex. 1005, 5, 7, 8, Figs. 4, 6–8); *id.* ¶¶ 171–173 (claim 11) (citing Ex. 1004 ¶¶ 43, 46; Ex. 1056, 667–668; Ex. 1047, 2386); *id.* ¶¶ 174–175 (claim 12) (citing Ex. 1004 ¶¶ 43, 46); *id.* ¶¶ 176–178 (claim 13) (citing Ex. 1004 ¶¶ 18, 32, 33, 36; Ex. 1005, 1, 4, 7); *id.* ¶¶ 179–181 (claim 14) (citing Ex. 1004, Abstract, ¶¶ 18, 32, 33, 36, 37; Ex. 1005, 1). Patent Owner does not present separate arguments for any of the dependent claims. *See generally* PO Resp. 37–46. We, therefore, adopt the teachings set forth in the Petition and in Dr. Spellman's Declaration as mapped to the limitations of the challenged claims as our own findings. *See In re NuVasive, Inc.*, 841 F.3d 966, 974 (Fed. Cir. 2016) (explaining that the Board need not make specific findings about claim limitations that a patent

owner does not dispute are disclosed in the prior art); *see also* Ex. 1002 ¶ 182 (Dr. Spellman's claim chart).

2. Motivation to combine/reasonable expectation of success

Even "[i]f all elements of the claims are found in a combination of prior art references," "the factfinder should further consider whether a person of ordinary skill in the art would [have been] motivated to combine those references, and whether in making that combination, a person of ordinary skill would have [had] a reasonable expectation of success." *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 833 (Fed. Cir. 2015). The "motivation to combine" and "reasonable expectation of success" factors are subsidiary requirements for obviousness subsumed within the *Graham* factors. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). We address motivation to combine and reasonable expectation of success in turn below.

a) Motivation to combine

Petitioner contends that an ordinarily skilled artisan would have had a reason to combine the teachings of Lu and Illumina, with a reasonable expectation of success, based on the teachings of the art, and based on the Lu and Illumina references themselves. Pet. 48–58. In our Institution Decision, we determined that Petitioner had shown sufficiently for institution that an ordinarily skilled artisan would have been motivated to modify Lu's system with Illumina's DASL assay. Inst. Dec. 27–28. Upon review of the complete record, we affirm our initial determination. We find that the preponderance of record evidence supports Petitioner's argument that an ordinarily skilled artisan would have regarded RT-PCR assays as old technology, readily replaced by the more advanced DASL assay. Pet. 51–58; Ex. 1002 ¶ 120. We also rely on and credit Dr. Spellman's testimony

that the DASL assay was "capable of investigating a substantially larger number of molecular targets simultaneously than RT-PCR." Ex. 1002 ¶ 120; *see also* Ex. 1047, 2386; Ex. 1053, 586; Pet. 52–53. In view of this evidence, we find that a preponderance of the evidence supports that an ordinary artisan would have been motivated to modify Lu's system with Illumina's DASL assay. We note that, during oral hearing, counsel for Patent Owner conceded that an ordinarily skilled artisan would have been motivated to use Illumina's DASL assay in Lu's system:

> JUDGE: . . . [W]hy wouldn't somebody skilled in the art just replace the chip, that Lu talks about, with a DASL assay chip?
>
> . . .
>
> MR. SINGER: . . . I think they have the better of the argument, there, to be perfectly blunt, that people would go to something that was a commercial product and use it. So, I will acknowledge that . . . .

Tr. 54:15–55:8.

b) Reasonable expectation of success

We next consider whether Petitioner has shown by a preponderance of the evidence that the skilled artisan would have had a reasonable expectation of success in achieving the method claimed in the '945 patent. "The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

We are persuaded that Petitioner has shown by a preponderance of the evidence that an ordinarily skilled artisan would have had a reasonable expectation of success using Illumina's DASL assay in Lu's system, given that the DASL assay was commercially available and recognized in the art

as useful for high-throughput expression analysis. *See* Pet. 54–58; *see also* Ex. 1002 ¶¶ 183–185; Ex. 1050, 28–29, 31; Ex. 1046, 2; Ex. 1048, 1806; Ex. 1049, 878. We also observe that all the elements of molecular profiling systems were known, and required only ordinary skill to carry out. *See* Pet. 56–58; *see also* Ex. 1002 ¶ 68, 186; Ex. 1037, Abstract; Ex. 1055, Abstract; Ex. 1051, 170, 172; Ex. 1032, 166, 169 (Table 2). Patent Owner does not provide specific arguments disputing Petitioner's position as to reasonable expectation of success. *See generally* PO Resp.; PO Sur-Reply; *see also* Reply 21 n.12.

3. Objective indicia of non-obviousness

We must consider any evidence of objective indicia of non-obviousness before reaching our conclusion on obviousness *vel non*. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016). Notwithstanding what the teachings of the prior art would have suggested to one of ordinary skill in the art at the time of the invention, the totality of the evidence submitted, including objective evidence of non-obviousness, may lead to a conclusion that the challenged claims would not have been obvious to one of ordinary skill. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). Patent Owner presents evidence of three of these considerations: (1) long-felt need, (2) skepticism/surprise (3) praise. PO Resp. 48–50.

a) Nexus

At the outset, we give Patent Owner's arguments about long-felt need and praise very little to no weight in our obviousness analysis. "For objective evidence of secondary considerations to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (quotation and emphasis omitted); *see also Fox*

Factory, Inc. v. SRAM, LLC, 944 F.3d 1366, 1373 (Fed. Cir. 2019) ("In order to accord substantial weight to secondary considerations in an obviousness analysis, the evidence of secondary considerations must have a nexus to the claims, i.e., there must be a legally and factually sufficient connection between the evidence and the patented invention." (quotation omitted)).

Here, Patent Owner also does not allege (or even mention) a "nexus" in its Response. *See* PO Resp. 14–24, 48–50. And this is not a case where we apply a presumption of nexus, because Patent Owner has not shown or alleged a specific product that is the invention disclosed and claimed in the '350 patent. *Id.*; *see also WBIP*, 829 F.3d at 1329 (setting forth circumstances in which the presumption of nexus applies); *Fox Factory*, 994 F.3d at 1373 (explaining that a nexus is presumed when "the patentee shows that the asserted objective evidence is tied to a specific product and that product 'embodies the claimed features, and is coextensive with them.'" (quoting *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1072 (Fed. Cir. 2018))).

In addition to a lack of nexus to the claimed invention, Patent Owner also fails to provide specific, persuasive evidence of long-felt need beyond a conclusory statement that "Drs. Von Hoff and Penny's invention fulfilled a long-felt need in the oncology community for improved tools for identifying therapeutic agents for their cancer patients." PO Resp. 49. This statement falls short of a preponderance of evidence that the claimed invention fulfills a long-felt need.

b) Bisgrove trial

In its Sur-Reply, Patent Owner alleges a nexus between the claims and the Bisgrove trial. PO Sur-Reply 25–28 (citing Ex. 2013[16]). Specifically, Patent Owner argues that "[t]he Bisgrove trial and its preceding abstract are strongly tied to the claimed system of the '350 patent." *Id.* at 26. According to Patent Owner, the "the oncology community initially expressed skepticism of the invention when it was first reported." PO Resp. 49. And it was not until the Bisgrove trial, "which Drs. Von Hoff and Penny conducted to gather clinical evidence in the face of that skepticism," Patent Owner argues, that the inventors "surprisingly demonstrated that their system worked." *Id.*

Although we have carefully considered Patent Owner's arguments and evidence, we again find that they fail to show nexus to the claimed invention. For example, Patent Owner argues that Drs. Von Hoff and Penny conducted the Bisgrove trial "using a treatment regimen selected by cancer-lineage independent molecular profiling of the patient's tumor." PO Resp. 17–18 (citing Ex. 2021 ¶¶ 37, 39). But Patent Owner fails to provide specific, persuasive evidence showing that the therapeutic agents used in the Bisgrove trial were, in fact, selected by a system embodied in the claims of the '350 patent. *See id.*; *see also* PO Sur-Reply 27 (citing Ex. 2021 ¶¶ 42–45). For example, neither Patent Owner nor Dr. O'Shaughnessy explain how Drs. Von Hoff and Penny used the limitations of claim 1 (e.g., a device, computer database, and computer-readable program codes) to generate a

[16] Daniel D. Van Hoff et al., Pilot Study Using Molecular Profiling of Patients' Tumors to Find Potential Targets and Select Treatments for Their Refractory Cancers, 28 (33) J. CLIN. ONCOL. 4877–83 (Nov. 20, 2010) ("the Bisgrove trial") (Ex. 2013).

report comprising a list of molecular targets and therapeutic agents. *See* PO Resp. 49; PO Sur-Reply 26–27; Ex. 2021 ¶¶ 37–45.

We also find Patent Owner's arguments and evidence insufficient to support skepticism and surprise. For example, Patent Owner relies on Dr. O'Shaughnessy's declaration as evidence of skepticism of the Bisgrove trial. PO Resp. 49 (citing Ex. 2021 ¶¶ 42–44). But during cross-examination, Dr. O'Shaughnessy admitted she cited no contemporaneous evidence for her opinion that oncologists were skeptical of the alleged invention, could not recall how many doctors she spoke with about the claimed invention, and could not answer how many of those doctors expressed skepticism. Ex. 1118, 210:2–212:20. We find that this testimony of Dr. O'Shaughnessy, many years after the fact and without corroboration, is entitled to little weight. *See Rohm & Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092 (Fed. Cir. 1997) ("Nothing in the rules or in our jurisprudence requires the fact finder to credit the unsupported assertions of an expert witness.").

For these reasons, we are not persuaded by Patent Owner's arguments that skepticism and surprise weigh toward the non-obviousness of the claimed subject matter.

4. Conclusion as to obviousness over Lu in view of Illumina

In sum, we find that the combination of Lu and Illumina teaches or suggests each and every element of claims 1–14. We find that an ordinarily skilled artisan would have been motivated to combine Lu with Illumina, and would have had a reasonable expectation of success in achieving the claimed invention. We also find that Patent Owner has failed to persuasively show secondary considerations of non-obviousness. As discussed above, we find that Patent Owner has not established the requisite nexus between the

challenged claims and any of the asserted secondary considerations. We are therefore unable to accord them any substantial weight. *Fox Factory*, 944 F.3d at 1373. Thus, after carefully considering the arguments and evidence, we determine that the record as a whole weighs in favor of a conclusion of obviousness, especially given the disclosures of the art of record in this case and strength of the obviousness case based on the first three *Graham* factors.

F. Petitioner's Remaining Grounds of Unpatentability

Our determination that Petitioner has demonstrated, by a preponderance of the evidence, that claims 1–14 would have been obvious over Lu and Illumina involves all challenged claims of the '350 patent. Thus, we need not address Petitioner's grounds of unpatentability based on obviousness of claims 2 and 3 over Lu, Illumina, and Muraca, Pet. 58–64, or obviousness of claims 7, 11, and 12 over Lu, Illumina, and McDoniels-Silvers, Pet. 64–68. *See, e.g.*, *Nippon Suisan Kaisha Ltd. v. Pronova Biopharma Norge AS*, PGR2017-00033, Paper 37 at 27 (PTAB Jan. 16, 2019) (citing *SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1359 (2019) (holding that a petitioner "is entitled to a final written decision addressing all of the claims it has challenged"); *Beloit Corp. v. Valmet Oy*, 742 F.2d 1421, 1423 (Fed. Cir. 1984) (holding that once a dispositive issue is decided, there is no need to decide other potentially dispositive issues)).

III. CONCLUSION[17]

Petitioner establishes by a preponderance of the evidence that claim 1–14 of the '350 patent are unpatentable as follows.

Claims	35 U.S.C. §	Reference(s)/Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
1–14	103(a)	Lu, Illumina	1–14	
2, 3	103(a)[18]	Lu, Illumina, Muraca		
7, 11, 12	103(a)[19]	Lu, Illumina, McDoniels-Silvers		
Overall Outcome			1–14	

[17] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. *See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

[18, 19] As explained above, we do not reach these alleged grounds of unpatentability. *Supra* § II.F.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–14 of the '350 patent have been proven to be unpatentable; and

FURTHER ORDERED that because this is a Final Written Decision, parties to the proceeding seeking judicial review of the Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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