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Paper No. 12
Entered: May 30, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FOUNDATION MEDICINE, INC.,
Petitioner,

v.

CARIS MPI, INC.,
Patent Owner.

Case IPR2019-00170
Patent 9,372,193 B2

Before CHRISTOPHER G. PAULRAJ, JACQUELINE T. HARLOW and KRISTI L. R. SAWERT, *Administrative Patent Judges.*

HARLOW, *Administrative Patent Judge.*

DECISION
Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Foundation Medicine, Inc. ("Petitioner") filed a Petition (Paper 3, "Pet."), requesting institution of an *inter partes* review of claims 1–14 of U.S. Patent No. 9,372,193 B2 (Ex. 1001, "the '193 patent"). Caris MPI, Inc. ("Patent Owner") timely filed a Preliminary Response (Paper 7, "Prelim. Resp."). Pursuant to our authorization (Paper 8), Petitioner filed a Reply to Patent Owner's Response (Paper 9, "Reply") and Patent Owner filed a Sur-Reply to Petitioner's Reply (Paper 10, "Sur-Reply").

Under 35 U.S.C. § 314(a), an *inter partes* review may not be instituted unless the information presented in the petition "shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." For the reasons stated below, we determine that there is a reasonable likelihood that Petitioner would prevail with respect to at least one challenged claim. We hereby institute *inter partes* review of the challenged claims on all the grounds of unpatentability asserted in the Petition.

A. Related Matters

The '193 patent is the subject of a co-pending district court proceeding, *Caris MPI, Inc. v. Foundation Medicine, Inc.*, Civil Action No: 1:17-cv-12194-MLW (D. Mass.). Pet. 2; Paper 4, 2. In addition, Petitioner has filed petitions seeking *inter partes* review of several other patents held by Patent Owner, including: IPR2019-00164 (U.S. Patent No. 8,880,350 B2), IPR2019-00165 (U.S. Patent No. 9,092,392 B2), IPR2019-00166 (U.S. Patent No. 9,292,660 B2), IPR2019-00171 (U.S. Patent No. 9,383,365 B2), and IPR2019-00203 (U.S. Patent No. 9,292,660 B2). We

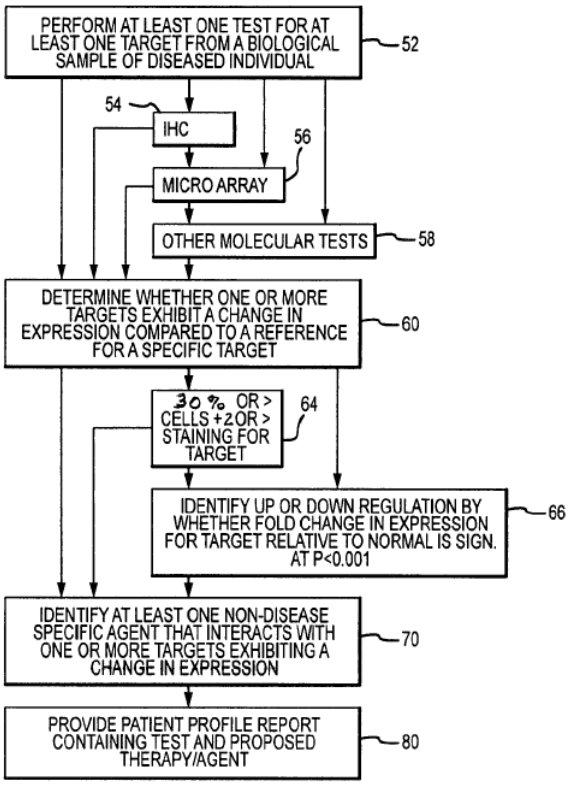
instituted *inter partes* reviews in IPR2019-00166 and IPR2019-00203 on May 14, 2019. *See* IPR2019-00166 (Paper 12); IPR2019-00203 (Paper 12).

B. The '193 Patent

The '193 patent, titled "System and Method for Determining Individualized Medical Intervention for a Disease State," issued on June 21, 2016. Ex. 1001, (54), (45). The '193 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 '193 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 . . . has been disease specific and not widely pursued." *Id.* at 1:45–48. The patent states that this 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 1:58–65. Thus, the '193 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 2:19–25, 2:30–35. The '193 patent states that this approach would provide patients "with a viable therapeutic alternative to those treatment regimens which currently exist." *Id.* at 2:25–29.

Figure 2 of the ’193 patent, reproduced below, provides an overview of an exemplary method for determining individualized medical intervention that utilizes a patient’s molecular profile. *Id.* at 5:4–7, 13:10–15.



In step 52, 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 13:19–25. Tests that may be performed include immunohistochemistry (IHC) analysis 54, microarray analysis 56, and/or any other known molecular tests 58. *Id.* at 13:25–35. The ’193 patent states that IHC analysis may be performed for such proteins as “Her2/Neu, ER, PR, c-kit, EGFR, MLH1, MSH2, CD20, p53, Cyclin D1, bcl2, COX-2, Androgen receptor, CD52, PDGFR, AR, CD25, and VEGF.” *Id.* at 2:64–3:4. The patent further discloses that microarray analysis may be

performed for myriad genes, including AR, EGFR, KIT, MLH1, PTEN, and PDGFRA. *Id.* at 3:5–23.

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 13:44–47. A change in expression may be observed via differential staining, the amount of overexpression or underexpression, and/or "by an absence of one or more genes, gene expressed proteins, molecular mechanisms, or other molecular findings." *Id.* at 13:47–66.

Next, "at least one non-disease specific agent is identified that interacts with each target having a changed expression in step 70." *Id.* at 14:1–4. The '193 patent states that a "non-disease specific agent is 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." *Id.* at 14:5–9.

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 14:25–27. The '193 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 12:50–58. The internal databases can include information about the patient biological sample, patient test results from molecular profiling, clinical data, and study protocols. *Id.* at 13:1–5. The external databases can include drug libraries,

gene libraries, disease libraries, and public databases such as GenBank. *Id.* at 13:5–9.

The ’193 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 4:4–24. The 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 4:45–49.

C. Challenged Claims

Petitioner challenges claims 1–14 of the ’193 patent. Claim 1, the sole independent claim of the ’193 patent, is illustrative, and is reproduced below:

> 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 molecular profile test values for the plurality of molecular targets, wherein the plurality of molecular targets comprises AR, EGFR, HER2, KIT, MLH1, PTEN, and PDGFRA; and
>
> b. at least one computer database comprising:
>
> i. a reference value for each of the plurality of molecular targets; and
>
> ii. a listing of available therapeutic agents for each of the plurality of molecular targets;
>
> c. a computer-readable program code comprising instructions to input the molecular profile test values and to

compare each of the molecular profile test values with a corresponding reference value from the at least one computer database 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 the comparison to the reference values 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 for which the comparison to the reference value indicated a likely benefit of the at least one therapeutic agent in (d) and the at least one therapeutic agent identified in (d).

D. Evidence Relied Upon

Petitioner relies upon the following references (Pet. 3, 16–22):

Lu	WO 03/017038 A2	Feb. 27, 2003	(Ex. 1004)
Muraca	US 2002/0150966 A1	Oct. 17, 2002	(Ex. 1006)

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

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 141–150 (2002) (Ex. 1007).

Petitioner also relies on the Declaration of Paul T. Spellman, Ph.D. (Ex. 1002).

E. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 3):

Claims	Basis	References
1–14	§ 103	Lu and Illumina
2, 3	§ 103	Lu, Illumina, and Muraca
7, 11	§ 103	Lu, Illumina, and McDoniels-Silvers

II. ANALYSIS

A. Level of Ordinary Skill in the Art

Petitioner contends that a person of ordinary skill in the art ("skilled artisan" or "POSA") for the '193 patent "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. 15–16 (citing Ex. 1002 ¶ 32). Patent Owner does not address the requisite level of skill in its Preliminary Response.

For purposes of this decision, we adopt Petitioner's presently undisputed definition of the level of ordinary skill in the art, as it is consistent with the level of skill in the art reflected in the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

B. Claim Construction

Based on the filing date of the Petition (November 5, 2018), the Board interprets claim terms in the '193 patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131,

2142–46 (2016).[1] Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Additionally, any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner does not propose any constructions for claim terms in the claim construction section of the Petition. Pet. 16. However, in its analysis for element (d) of claim 1, Petitioner contends that "the broadest reasonable interpretation of '***likely benefit*** of the at least one therapeutic agent' is any therapeutic agent with potential efficacy." Pet. 33 (citing Ex. 1002 ¶ 140). Additionally, Petitioner contends that "a POSA would understand claim element (d) ***not*** to require a therapeutic agent for any particular molecular target because claim element (d) only recites 'at least one therapeutic agent' from the 'listing of available therapeutic agents for the plurality of molecular targets.'" *Id.* at 33–34 (citing Ex. 1002 ¶ 141.).

In this regard, Petitioner points out that the "specification discloses no drug-efficacy correlations for several of the genes listed in the claimed panel," and that claim language of element (d) is open-ended due to the term

[1] A recent amendment to this rule changing the claim construction standard does not apply here because the Petition was filed before the November 13, 2018, effective date. *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).

"compris[ing]." *Id.* at 34. Thus, reasons Petitioner, claim element (d) would be understood "to mean the claimed system has the computer-implemented capacity to access test and reference values in a database and to cross-reference molecular targets exhibiting a difference in test and reference values with a therapeutic agent database that includes information associating agents with one or more molecular targets." *Id.* (citing Ex. 1002 ¶ 141).

Patent Owner does not address the foregoing arguments in its Preliminary Response, nor does it propose any of its own claim constructions for other claim terms. Prelim. Resp. 16–17.

As it is undisputed at this stage, we will accept Petitioner's proposed interpretation of claim element (d) in our analysis as to whether there is a reasonable likelihood that Petitioner would prevail with respect to at least one challenged claim.[2] We request the parties to further address this claim construction issue in their post-institution briefs.

C. Obviousness Based on Lu and Illumina

Petitioner contends that claims 1–14 are rendered obvious by the combined teachings of Lu and Illumina. Pet. 23–57. To support its contentions, Petitioner cites to Dr. Spellman's declaration testimony (Ex. 1002). Patent Owner disagrees, and asserts that Illumina does not qualify as prior art. Prelim. Resp. 18–28. Patent Owner further contends

[2] In this regard we note Petitioner's currently unrebutted assertion, discussed *infra*, that "there were already therapeutic agent(s) with potential efficacy associated with each recited gene prior to May 18, 2006." Pet. 34 n.7.

that the combination of Lu and Illumina fails to teach identifying cancer therapies independent of cancer type. *Id.* at 28–35. For the reasons provided below, we determine that Petitioner has demonstrated a reasonable likelihood of prevailing on its assertion that claims 1–14 are unpatentable based on the combination of Lu and Illumina.

1. Overview of Lu

Lu is an International Patent Application, published under the Patent Cooperation Treaty. Ex. 1004, (12). Lu discloses a "computerized decision support system for selecting the optimum treatment for human cancer." *Id.* at (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. Overview of Illumina

Illumina is a technical bulletin prepared by Illumina, Inc. Ex. 1005. 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 collected from ten publicly available cancer 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.

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 measured 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. Prior Art Status of Illumina

Under 35 U.S.C. § 311(b), a petitioner in an *inter partes* review may challenge the claims of a patent only on the basis of "prior art consisting of patents or printed publications." At the institution stage, the Board has required the petitioner to make a "threshold showing" that any reference relied upon was publicly accessible prior to the effective filing date of the challenged patent. *See, e.g.*, *Frontier Therapeutics, LLC v. Medac Gesellschaft Für Klinische Spezialpräparate mbH*, IPR2016-00649, slip op. at 22 (PTAB Sept. 1, 2016) (Paper 10) (denying trial institution upon finding that petitioner failed to make a threshold showing that an alleged "printed

package insert" was a printed publication); *Instradent USA, Inc. v. Nobel Biocare Servs. AG*, IPR2015-01786, slip op. at 16–17 (PTAB Feb. 19, 2016) (Paper 14) (finding that deposition testimony from the challenged patent's co-inventor stating that hundreds of copies of a catalog may have been printed and distributed to customers was sufficient to make a threshold showing of public accessibility; granting trial institution).

Here, we are persuaded that Petitioner has made the requisite threshold showing that Illumina is a prior art printed publication for purposes of institution. As noted by Petitioner, the Illumina reference itself bears indicia that it was likely published, including a publication date (November 16, 2005) and a publication number (470-2005-003). *See* Pet. 20; Reply 3–5. Moreover, Illumina is identified as a "technical bulletin," akin to a product catalog, which "is the type of document intended for public dissemination, and it bears no designations, such as 'draft' or 'confidential,' that might suggest that it was not intended for public distribution." *See Nobel Biocare Servs. AG v. Instradent USA, Inc.*, 903 F.3d 1365, 1377 (Fed. Cir. 2018). In addition to the dates and markings on the document itself, Petitioner has pointed to the declaration of the Internet Archive's Office Manager, Christopher Butler, attesting that the Illumina publication was archived by the Wayback Machine on December 27, 2005, and thereby confirming that it was publicly available. Ex. 1024, 5; Pet. 20; Reply 2–3.

Patent Owner argues that the Butler declaration and attached Wayback Machine printouts are insufficient to establish the public accessibility of the Illumina reference because "Petitioner fails to mention

[the Butler declaration] anywhere in its Petition outside the exhibit list," and this evidence should therefore not be considered in our institution analysis. Prelim. Resp. 21. We are not persuaded by this argument. As an initial matter, we observe that Petitioner cited to Exhibit 1024 in its Petition as the "Affidavit of Christopher Butler," immediately after stating that "Illumina is prior art under § 102(a)." Pet. 20. Moreover, we gave the parties a sufficient opportunity to address the Butler declaration in additional briefing (both a Reply and Sur-Reply). Paper 8. We have considered the arguments presented in those briefs in determining whether Petitioner has made a sufficient showing for institution.

Patent Owner further argues that, even if the Butler declaration were considered, it fails to show that the Illumina reference was available to persons of skill at the relevant time because there is no showing that the skilled artisan could have searched for, and found, the reference on the Internet without already having the exact URL where it was published. Prelim. Resp. 21–24. Patent Owner contends that there is no indication that the product page shown on the archived webpage (Ex. 1024, 4) linked directly to the version of the Illumina reference appearing in the Butler declaration (*id.* at 6–13). Prelim. Resp. 23. Patent Owner also contends that the Petition fails to meet the standard set forth in *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1349–50 (Fed. Cir. 2016). Prelim. Resp. 24–28; Sur-Reply 1.

We do not interpret Federal Circuit precedent as suggesting that only certain types of evidence may be used to show public accessibility of a webpage. To the contrary, whether a reference is a "printed publication" is a

"case-by-case inquiry into the facts and circumstances surrounding the reference's disclosure to members of the public." *Jazz Pharm., Inc. v. Amneal Pharm., LLC*, 895 F.3d 1347, 1356 (Fed. Cir. 2018) (citing *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004)). In *Jazz Pharmaceuticals*, the Federal Circuit made clear that "neither indexing nor searchability" was required to determine that an online document was publicly accessible. *Id.* at 1359. Here, we find on the current record that the relevant public, including those skilled in the art, would have been generally aware that Illumina, Inc., offered research tools used for gene expression assays. *See* Ex. 1047, 2384 (describing Illumina's DASL assay). That would seem to provide enough of a reason for anyone interested in the DASL assay to look at Illumina's website, where technical bulletins such as the Illumina reference could be accessed.

We find Patent Owner's remaining arguments largely go to the question of whether Petitioner has met its ultimate burden of proving that the Illumina reference was publicly accessible. But we need not answer that question at this stage. Rather, based on the present record, we find that Petitioner has made a sufficient threshold showing that Illumina qualifies as a prior art printed publication for institution. To the extent Patent Owner continues to challenge the printed publication status of Illumina after institution, the parties may further develop the record on this issue. We will make our determination as to whether Petitioner has satisfied its burden of proving public accessibility in our final written decision based on the entire record.

4. Rationale for and Reasonable Expectation of Success in Combining Lu and Illumina

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).

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. 47–57. At this stage of the proceeding, Patent Owner does not provide specific arguments as to motivation to combine and reasonable expectation of success. *See generally* Prelim. Resp.

Upon review of the record, we are satisfied that Petitioner has shown sufficiently for institution that an ordinarily skilled artisan would have had a reason to combine the disclosures of Lu and Illumina to provide an improved molecular-profiling system for identifying therapeutic drugs based on a patient's genotype. The record reasonably supports Petitioner's argument that, before May 18, 2006, "it was a common goal of many researchers in the field of personalized medicine to obtain comprehensive

molecular profiles of individuals to provide more effective diagnostic and therapeutic options" to patients. Pet. 48; *see* Ex. 1002 ¶¶ 112–13; Ex. 1050, 27–28. The record also reasonably supports Petitioner's argument that an ordinarily skilled artisan would have been aware of multiple techniques for obtaining molecular profile information, as well as multiple databases tying therapies to genetic markers. Pet. 48–49; *see* Ex. 1002 ¶¶ 114–115, 117; Ex. 1050, 30; Ex. 1051, 170–171.

Finally, the record reasonably 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. 51–53; Ex. 1002 ¶ 119. Specifically, we rely on Dr. Spellman's currently unrebutted testimony that the DASL assay was "capable of investigating a substantially larger number of molecular targets simultaneously than RT-PCR." Ex. 1002 ¶ 119; *see also* Ex. 1047, 2386; Ex. 1053, 586; Pet. 52–53.

Thus, in view of the background knowledge in the art and the specific teachings of Lu and Illumina, we are satisfied that this record supports a reasonable likelihood that an ordinarily skilled artisan would have been motivated to modify Lu's system with Illumina's DASL assay.

We are also satisfied that the ordinarily skilled artisan would have had a reasonable expectation of success, given that the DASL assay was commercially available and apparently recognized in the art as useful for high-throughput expression analysis. *See* Pet. 54–57; *see also* Ex. 1002 ¶¶ 68, 182–186; Ex. 1050, 28–29, 31; Ex. 1046; Ex. 1047, 2386; 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. 56–57; *see also* Ex. 1002 ¶¶ 68, 186; Ex. 1037, Abstract; Ex. 1055, Abstract; Ex. 1051, 170, 172; Ex. 1032, 166, 169 (Table 2).

5. Claim 1

Petitioner asserts that each element of claim 1 is taught or suggested by the combination of Lu and Illumina. For example, Petitioner contends that Lu teaches "[a] system for generating a report identifying at least one therapeutic agent for an individual with a cancer" (Ex. 1001, 17:3–3), as recited in the preamble of claim 1. Specifically, Petitioner contends that Lu discloses identifying "which drugs are optimum to treat other cancerous conditions in patents" and providing a "computerized decision support system" for recommending the "optimum anti-cancer drug to prescribe for a patient" as objects of the invention. Pet. 23 (quoting Ex. 1004 ¶¶ 15–16 (internal quotation marks omitted)).

Element (a) of claim 1 calls for "at least one device configured to assay a plurality of molecular targets in a biological sample to determine molecular profile test values for the plurality of molecular targets, wherein the plurality of molecular targets comprises AR, EGFR, HER2, KIT, MLH1, PTEN, and PDGFRA." Ex. 1001, 17:4–9. Petitioner asserts that the combination of Lu and Illumina teaches this claim element. Pet. 23–27. For example, Petitioner contends that Lu discloses a system for assaying a patient sample in order to produce test values for multiple targets by quantifying the up- and down-regulation of the targets. *Id.* at 24 (citing Ex. 1004 ¶¶ 18, 19, 22, 34, 35, 51, 52; Ex. 1002 ¶ 125). Petitioner also points out that Lu discloses assaying EGFR and HER2, two of the molecular targets recited in claim 1. *Id.* at 17–18, 25 (citing Ex. 1004 ¶¶ 22, 48, 51, 53,

54; Ex. 1002 ¶¶ 100, 101). Concerning Illumina, Petitioner asserts that reference discloses the DASL Assay, which allows determination of expression values for nucleic acid sequence targets that correspond to 502 cancer-related genes, including AR, EGFR, HER2, KIT, MLH1, PTEN, and PDGFRA. *Id.* at 25–26 (citing Ex. 1005, Table 1).

Element (b) of claim 1 further recites "at least one computer database comprising: i. a reference value for each of the plurality of molecular targets; and ii. a listing of available therapeutic agents for each of the plurality of molecular targets." Ex. 1001, 17:10–14. Petitioner asserts that the combination of Lu and Illumina teaches this claim element. Pet. 27–31. According to Petitioner, Lu discloses a computerized decision support system that compares expression levels obtained from a patient sample to a reference value, and quantifies any difference between the sample and reference values. *Id.* at Pet. 20–30 (citing Ex. 1004 ¶¶ 18, 50, 51; Ex. 1002 ¶¶ 131–133). Petitioner further asserts that Lu's decision support system comprises a gene and drug database updated to include novel therapeutic agents and associations of therapeutic agents with genotypes. Pet. 27–28, 30–31 (citing Ex. 1004 ¶¶ 4, 18, 44, Fig. 4; Ex. 1002 ¶¶ 130, 131, 134). Petitioner contends also that Illumina discloses comparing test expression values derived from a cancerous sample to reference values from a normal sample. *Id.* at 31–32 (citing Ex. 1005, 5, 7, Figs. 4, 6, 7; Ex. 1002 ¶¶ 132, 133).

Element (c) of claim 1 requires "a computer-readable program code comprising instructions to input the molecular profile test values and to compare each of the molecular profile test values with a corresponding

reference value from the at least one computer database in (b)(i)." Ex. 1001, 17:15–19. Petitioner points to several of the same teachings of Lu set forth *supra*, concerning claim element (b), as disclosing this claim element. Pet. 31–32. In particular, Petitioner points to Lu's disclosure of 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 . . . ; a database describing the correlation of patient genotypes and the efficacy and toxicity of various anticancer 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. at 31 (quoting Ex. 1004 ¶ 18) (internal quotation marks omitted). Petitioner also explains that Lu discloses exemplary results of correlating and calculating expression levels for certain cancer-related genes, and interpreting that data according to criteria stored in the database. *Id.* at 31 (citing Ex. 1004 ¶¶ 23, 50, 51, Fig. 4). Petitioner further asserts that a "POSA reading Lu would have understood that these qualitative and quantitative examples disclose that target expression levels from an assayed sample are correlated relative to a reference." *Id.* at 32 (citing Ex. 1002 ¶ 135).

In element (d), claim 1 further recites:

> 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 the comparison to the reference values in (c) indicates a likely benefit of the at least one therapeutic agent.

Ex. 1001, 17:20–26. Under the broadest reasonable interpretation, discussed above, Petitioner contends that an ordinarily skilled artisan would understand this limitation to require the claimed system "to access test and reference values in a database and to cross-reference molecular targets exhibiting a difference in test and reference values with a therapeutic agent database that includes information associating agents with one or more molecular targets." Pet. 34. (citing Ex. 1002 ¶ 141). According to Petitioner, 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.

Pet. 34–35 (quoting Ex. 1004, Abstract). Petitioner reasons that "[i]n associating the patient's 'genotype,' Lu's 'computerized decision system' uses data corresponding to 'multiple gene[detection], expression[levels,] and/or mutations associated with a particular cancer' to select recommended therapies." *Id.* at 35 (quoting Ex. 1004 ¶ 38). Pointing to Figure 4 of Lu, and the related discussion, Petitioner further asserts that Lu teaches a "computerized system for accessing test and reference values in a database and cross-referencing molecular targets exhibiting a difference in test and reference values with a therapeutic agent database that includes information associating molecular targets with therapies known to have potential efficacy against those targets." *Id.* (citing Ex. 1004 ¶¶ 45–46, Fig. 4; Ex. 1002 ¶ 142).

Finally, element (e) of claim 1 recites "a computer-readable program code comprising instructions to generate a report that comprises a listing of the molecular targets for which the comparison to the reference value indicated a likely benefit of the at least one therapeutic agent in (d) and the at least one therapeutic agent identified in (d)." Ex. 1001, 17:27–32. Petitioner 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. 36 (citing *Praxair Distribution, Inc. v. Mallinckrodt Hosp. Prods. IP Ltd.*, 890 F.3d 1024, 1032 (Fed. Cir. 2018)). But, in the event limitation (e) is given patentable weight, then Petitioner asserts that Lu discloses this claim element. *Id.* at 36–37 (citing Ex. 1002 ¶¶ 143–44). For example, Petitioner asserts that "Lu discloses that the bioinformatic software running on the computer incorporates both the test values of the molecular targets, their comparison to reference values, and the resulting indicated likely benefit from at least one therapeutic, which is subsequently translated into the final 'plain language' read-out." *Id.* at 37 (citing Ex. 1004 ¶¶ 32, 50).

Based on our review of the current record, and in light of our preliminary claim construction, we agree with Petitioner's characterization of the teachings of Lu and Illumina, and the knowledge in the art, as well as Petitioner's assertions as to the reasonable inferences an ordinary artisan would have made from those references.

Patent Owner does not, at this stage, dispute Petitioner's characterization of the cited teachings of Lu and Illumina, but rather, asserts that the combination of Lu and Illumina does not render claim 1 obvious

because it does not identify cancer therapies independent of cancer type. Prelim. Resp. 28–35. According to Patent Owner, the inventors of the '193 patent "invented and patented a novel system of performing molecular profiling of tumors to identify treatment options *independent of cancer type*, based on groups of molecular targets *not traditionally or conventionally* associated with a specific type of cancer." *Id.* at 5 (emphases added). In Patent Owner's view, therefore, Petitioner must establish that the combination of Lu and Illumina teaches or suggests the identification of cancer therapies independent of cancer type in order to prevail on its obviousness challenge. *Id.* at 28–35.

We do not find Patent Owner's contentions persuasive on this record. At this juncture, we see nothing in the plain language of claim 1 that limits the claimed system to the identification of therapeutic agents "not previously associated with treating the patient's diagnosed disease," i.e., a non-disease specific therapeutic agent. *See* Ex. 1001, 14:5–9; *see also id.* at 17:2–32. Rather, we understand the claim as more broadly addressed to determining the molecular profile for an individual with a cancer, and generating a report identifying at least one therapeutic agent indicating a likely benefit based on that individual's molecular profile—irrespective of any known association between the therapeutic agent and the particular cancer with which the patient has been diagnosed.

Claim 1 recites a plurality of molecular targets comprising AR, EGFR, HER2, KIT, MLH1, PTEN, and PDGFRA. *Id.* at 17:8–9. At this stage of the proceeding, we rely on the teachings of Lu and Illumina, as well as Dr. Spellman's currently unrebutted testimony, that each of these

molecular targets was known in the art to be associated with cancer. *See* Ex. 1004 ¶ 22; Ex. 1005, 4 (Table 1); Ex. 1002 ¶¶ 84–86, 125–129. Claim 1 also recites "a listing of available therapeutic agents for" these molecular targets, which, according to the '193 patent, are therapeutic agents known to interact with the molecular targets. Ex. 1001, 4:17–24, 14:1–10. And, although the preamble of claim 1 recites "identifying at least one therapeutic agent for an individual with a cancer," the claim does not address any relationship between the identified therapeutic agent and the cancer. *Id.* at 17:2–32; *see also* Prelim. Resp. 16. Thus, it appears to us on this record that claim 1 encompasses a system that compares a patient's molecular profile to known therapies for known molecular targets—whether or not those known therapies were traditionally associated with treating cancer. We request the parties to further address this claim interpretation issue in their post-institution briefs to the extent either party disagrees.

Moreover, on this record and at this stage of the proceeding, we do not read Lu as narrowly as Patent Owner contends. Lu 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. Taken together with Lu's teaching that the effectiveness of a particular drug can vary "from patient to patient"—even patients within the same patient group, *id.* ¶ 3—this statement appears to teach that Lu's system determines therapy based on the individual patient's genotype, rather than that patient's

cancer type. In any event, although we acknowledge Patent Owner's argument that this teaching merely shows that "it is possible to analyze tumors other than breast cancer tumors," that argument is not persuasive on this record in the absence of evidentiary or expert testimony support. *See* Prelim. Resp. 31.

Based on the foregoing, we conclude that Petitioner has established a reasonable likelihood that it will prevail on its assertion that the combination of Lu and Illumina renders obvious claim 1 of the '193 patent.

6. Claims 2–14

Petitioner asserts that the combination of Lu and Illumina renders obvious claims 2–14, which depend from claim 1. *See* Pet. 37–57. Relying on the cited teachings of Lu and Illumina, and the cited testimony of Dr. Spellman, Petitioner sufficiently accounts for the limitations recited in each of dependent claims 2–14, and the claims as a whole. *See id.* Patent Owner does not address Petitioner's showing.

Based on the preliminary record, and for the reasons already set forth with regard to claim 1, as well as the analysis set forth at pages 37–57 of the Petition, we are persuaded that Petitioner has shown sufficiently at this stage in the proceeding that there is a reasonable likelihood that it will prevail in establishing the unpatentability of dependent claims 2–14 over the combination of Lu and Illumina.

D. Obviousness Based on Lu, Illumina, and Muraca

Petitioner contends that claims 2 and 3 are rendered obvious by the combined teachings of Lu, Illumina, and Muraca. Pet. 57–63. At this juncture, Patent Owner does not separately address the merits of Petitioner's

challenge based on the combination of Lu, Illumina, and Muraca, but relies instead on the same arguments discussed above concerning the combination of Lu and Illumina. Prelim. Resp. 35.

1. Overview of 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 related 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.

2. Claims 2 and 3

Claims 2 and 3 depend from claim 1 and respectively require that the "molecular profile test values are input into the system" either "from a location that is remote from the at least one computer database" (claim 2) or "over an internet connection" (claim 3). Petitioner asserts that Muraca discloses a system that permits remote users to access and add to information in a specimen-linked database via a network-connected internet browser, and, therefore, satisfies these claim elements. Pet. 58–60 (citing Ex. 1002 ¶¶ 197, 201; Ex. 1006 ¶¶ 18–19, 125, 151, 190). Petitioner further contends that an ordinarily skilled artisan would have had reason for, and a reasonable expectation of success in combining Lu, Illumina, and Muraca. Pet. 60–63.

As explained above, at this stage, Patent Owner does not separately address Petitioner's challenge based on the combination of Lu, Illumina, and Muraca. For the reasons already set forth with regard to claim 1, as well as the analysis set forth at pages 57–63 of the Petition, we are persuaded that Petitioner has shown sufficiently at this stage in the proceeding that there is a reasonable likelihood that it will prevail in establishing the unpatentability of claims 2 and 3 based on the combination of Lu, Illumina, and Muraca.

E. Obviousness Based on Lu, Illumina, and McDoniels-Silvers

Petitioner contends that claims 7 and 11 are rendered obvious by the combined teachings of Lu, Illumina, and McDoniels-Silvers. Pet. 63–67. At this juncture, Patent Owner does not separately address the merits of Petitioner's challenge based on the combination of Lu, Illumina, and

McDoniels-Silvers, but relies instead on the same arguments discussed above concerning the combination of Lu and Illumina. Prelim. Resp. 35.

1. Overview of 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.*

2. Claims 7 and 11

Claims 7 and 11 depend from claim 1 and respectively require that the "molecular profile test values for the plurality of molecular targets are determined after the individual has received drug therapy for the cancer" (claim 7) and "wherein the individual has been treated by and failed to respond to at least one cancer therapeutic" (claim 11). Petitioner asserts that McDoniels-Silvers satisfies these claim elements because it discloses screening samples from patients with prior cancers, from a cancer previously treated with radiation, and from a cancer previously treated with

chemotherapy five times. Pet. 63–64 (citing Ex. 1002 ¶¶ 214, 218; Ex. 1007, Table 1 ¶¶ 18–19, 125, 151, 190). Petitioner further contends that an ordinarily skilled artisan would have had reason for, and a reasonable expectation of success in, combining Lu, Illumina, and McDoniels-Silvers. Pet. 64–67.

As explained above, at this stage, Patent Owner does not separately address Petitioner's challenge based on the combination of Lu, Illumina, and McDoniels-Silvers. For the reasons already set forth with regard to claim 1, as well as the analysis set forth at pages 63–67 of the Petition, we are persuaded that Petitioner has shown sufficiently at this stage in the proceeding that there is a reasonable likelihood that it will prevail in establishing the unpatentability of claims 7 and 11 based on the combination of Lu, Illumina, and McDoniels-Silvers.

III. CONCLUSION

For the foregoing reasons, we determine that the Petition and evidence in this record at this stage establish that there is a reasonable likelihood that Petitioner would prevail with respect to at least one of the claims challenged in the Petition. We therefore grant the Petition and institute trial as to all challenged claims on all grounds stated in the Petition. At this juncture, we have not made a final determination with respect to the patentability of the challenged claims, nor with respect to claim construction.

IV. ORDER

Accordingly, it is hereby:

ORDERED that *inter partes* review of claims 1–14 of the ’193 patent is instituted on all grounds in the Petition; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; the trial will commence on the entry date of this decision.

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