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Paper No. 12
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FOUNDATION MEDICINE, INC.,
Petitioner,

v.

CARIS MPI, INC.,
Patent Owner.

Case IPR2019-00164
Patent 8,880,350 B2

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

SAWERT, *Administrative Patent Judge.*

DECISION
Granting Institution of *Inter Partes* Review
37 C.F.R. § 42.108

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. 8,880,350 B2 (Ex. 1001, "the '350 patent"). Caris MPI, Inc. ("Patent Owner") timely filed a Preliminary Response (Paper 7, "Prelim. Resp."). On our authorization (Paper 8), Petitioner filed a Reply to Patent Owner's Preliminary Response (Paper 9, "Reply") and Patent Owner filed a Sur-Reply to Petitioner's Reply (Paper 10, "Sur-Reply").

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314(b); 37 C.F.R. § 42.4(a). We may not institute an *inter partes* review "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). On April 24, 2018, the Supreme Court held that a decision to institute under 35 U.S.C. § 314(b) may not institute review on fewer than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1355–56 (2018). Also, in accordance with USPTO Guidance, "if the PTAB institutes a trial, the PTAB will institute on all challenges raised in the petition." *See Guidance on the Impact of SAS on AIA Trial Proceedings* (April 26, 2018) (available at https://www.uspto.gov/patents-application-process/patent-trial-and-appealboard/trials/guidance-impact-sas-aia-trial).

Applying those standards, and upon consideration of the information presented in the Petition, Preliminary Response, Reply, and Sur-Reply, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least one claim of the '350 patent is unpatentable.

Accordingly, we institute an *inter partes* review of all challenged claims (1–14) of the ’350 patent, based on all grounds raised in the Petition.

II. BACKGROUND

A. *Related Proceedings*

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. The following proceedings, before the Board, 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). Trials were instituted in IPR2019-00166 and IPR2019-00203 on May 14, 2019. *See* IPR2019-00166 (Paper 12); IPR2019-00203 (Paper 12).

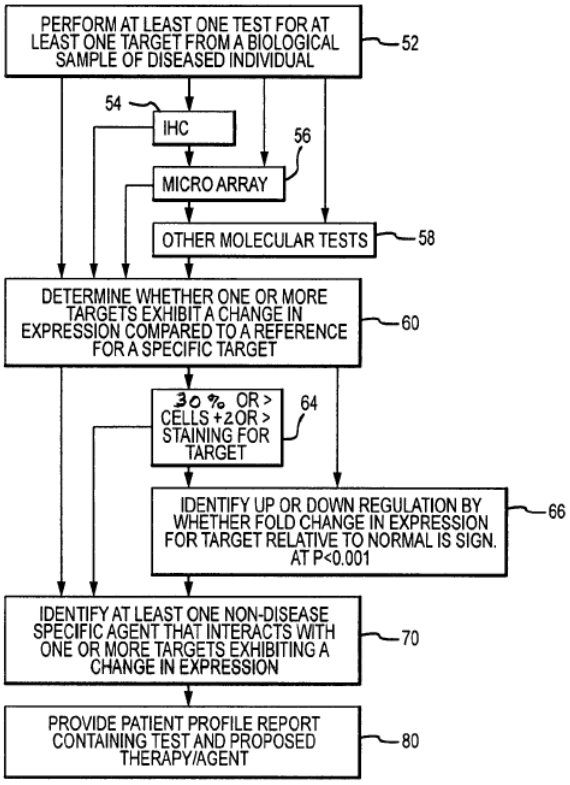
B. *The ’350 patent*

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 . . . has been disease specific and not widely pursued.” *Id.* at 1:42–46. The ’350 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 1:55–62. 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 method for determining individualized medical intervention that utilizes a patient's molecular profile. *Id.* at 5:1–4, 13:7–12.



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 13:15–21. 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 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. 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.

C. *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).

Id. at 16:64–17:27.

D. *The Prior Art*

Petitioner advances the following references as prior art on which it relies for the asserted grounds challenging the claims of the ’350 patent:

1. Mou-Ying Fu Lu and Rong Yu, WO 03/017038 A2 (Feb. 27, 2003) (“Lu,” Ex. 1004);

2. Illumina® Gene Expression Profiling, Technical Bulletin, *RNA Profiling with the DASL® Assay* (2005) (“Illumina,” Ex. 1005);

3. Patrick J. Muraca, U.S. Patent Application Publication No. 2002/0150966 A1 (Oct. 17, 2002) (“Muraca,” Ex. 1006); and

4. 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).

E. *Asserted Grounds of Unpatentability*

Petitioner challenges the patentability of the '350 patent's claims on the following three grounds:

References	**Basis**	**Claims challenged**
Lu and Illumina	§ 103(a)	1–14
Lu, Illumina, and Muraca	§ 103(a)	2 and 3
Lu, Illumina, and McDoniels-Silvers	§ 103(a)	7, 11, and 12

Pet. 3–4. Petitioner also relies on the Declaration of Paul T. Spellman, Ph.D. (Ex. 1002). *Id.* at 4.

III. ANALYSIS

We organize our analysis into four sections. First, we address the level of ordinary skill in the art. Second, we address claim construction. Third, we provide an overview of the asserted references. And fourth, taking account of the information presented, we consider whether the grounds asserted in the Petition meet the threshold showing for instituting an *inter partes* review under 35 U.S.C. § 314(a).

A. *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. Petitioner contends,

and Dr. Spellman testifies, 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). Patent Owner does not address the requisite level of skill in its Preliminary Response.

We adopt Petitioner's definition for our analysis in this decision, because it is consistent with the level of ordinary skill reflected in the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001). Further, based on the information presented at this stage of the proceeding, we consider Petitioner's declarant, Dr. Spellman, qualified to opine about the perspective of an ordinary artisan at the time of the invention. *See* Ex. 1002 ¶¶ 4–15.

B. *Claim Interpretation*

Based on the filing date of the Petition (November 6, 2018), the Board interprets claim terms in the '350 patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. *See* 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016) (upholding the use of the broadest reasonable interpretation standard).[1]

[1] On October 11, 2018, the USPTO revised its rules to harmonize the Board's claim construction standard for interpreting claims in trial proceedings before the Patent Trial and Appeal Board with the standard used in federal district court. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal

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); *see also TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016) ("Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history.").

Petitioner does not propose any constructions for claim terms. Pet. 16–17. In its analysis for element (d) of claim 1, however, 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. 34 (citing Ex. 1002 ¶ 141). Petitioner further contends that an ordinarily skilled artisan "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 34–35 (citing Ex. 1002 ¶ 142).

Additionally, Petitioner contends that "plurality of molecular targets" in element (d) is open-ended because the claim recites "comprises," and thus, the skilled artisan would understand "element (d) 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

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Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018) (to be codified at 37 C.F.R. pt. 42). This rule change, however, applies to petitions filed *on or after November 13, 2018*, and, therefore, does not apply to this proceeding. *Id*.

difference in test and reference values with a therapeutic agent database that includes information associating agents with one or more molecular targets." *Id.* at 35 (citing Ex. 1002 ¶ 142 n.8).

Patent Owner does not address the foregoing arguments in its Preliminary Response, nor does it propose any of its own interpretations for other claim terms. Prelim. Resp. 14–15.

Because the broadest reasonable interpretation of claim element (d) is undisputed at this stage, we accept Petitioner's proposed interpretation 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 interpretation issue in their post-institution briefs.

We determine that we need not expressly interpret any other claim term for this decision. *See 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 necessary to resolve the controversy.").

C. *Asserted References*

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

[2] In this regard, we note Petitioner's currently unrebutted assertion that "there were already therapeutic agent(s) with potential efficacy associated with each recited gene prior to May 18, 2006." Pet. 35, n.5.

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. 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.

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.*

D. *Illumina as a "Printed Publication"*

Before turning to Petitioner's asserted grounds of unpatentability, we address Patent Owner's threshold argument that Petitioner has failed to establish that Illumina qualifies as a printed publication. Prelim. Resp. 18–28. Under 35 U.S.C. § 311(b), a petitioner in an *inter partes* review may challenge the claims of a patent only on "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. 21–23. 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). 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.

E. *Asserted Ground of Unpatentability Based on Lu in View of Illumina*

Petitioner contends that claims 1–14 are unpatentable as obvious over Lu and Illumina. Pet. 23–58. Specifically, Petitioner argues that the combination of Lu and Illumina teaches or suggests each limitation of those claims. *Id.* at 23–48. Relying on the Declaration of Dr. Spellman, Petitioner also argues that a person of ordinary skill in the art would have been motivated to combine the references, and would have had a reasonable expectation of success. *Id.* at 48–58 (citing Ex. 1002 ¶¶ 113–24, 68, 147, 183–87). Patent Owner opposes. Prelim. Resp. 17–35.

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time of the invention to a person having ordinary skill in the art. *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: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

Having considered the arguments and evidence before us, we find that the record establishes a reasonable likelihood that Petitioner would prevail on at least one claim on its asserted ground of obviousness as to Lu in view of Illumina.

1. *The claimed limitations*

Upon review of the record, we are satisfied that Petitioner establishes sufficiently for institution that the proposed combination of Lu and Illumina

teaches or suggests each limitation of the challenged claims. *See* Pet. 23–38. For institution, therefore, we agree with and adopt Petitioner's arguments and supporting evidence mapping the language of claims 1–14 to the teachings of Lu and Illumina. *Id.*; Ex. 1002 ¶ 182.

We focus our analysis on claim 1 here. 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, on this record and for institution, 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). We also observe that Lu teaches that the "recommendation" may be in the form of a printed-out 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 subpart (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, on this record and for institution, 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[3]) and EGFR (also known as ERBB1[4]), 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 "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, on this record and for institution, that Lu discloses a computer database with biological profile data that includes reference values 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

[3] *See* Ex. 1060.
[4] *See* Ex. 1044.

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. We agree with Petitioner, on this record and for institution, 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, on this record and for institution, 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 "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, on this record and for institution, Petitioner argues 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" "correlate[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:

> 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. Under the broadest reasonable interpretation, discussed above, Petitioner argues that an ordinarily skilled artisan would understand this limitation to require a system to access test and reference values, and to cross-reference molecular targets with a therapeutic agent database that associates agents with one or more molecular targets. *Id.* at 34–35 (citing Ex. 1002 ¶¶ 141–42). Accepting that interpretation for institution, we agree with Petitioner, on this record, that Lu adequately 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. *Id.*

Finally, claim 1 recites "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 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)). But, in the event limitation (e) is given patentable weight, then Petitioner asserts that Lu discloses the creation of a patient profile report that includes test results for various targets and proposed therapies. *Id.* at 37–38 (citing Ex. 1002 ¶¶ 44–45).

We are satisfied that Petitioner establishes sufficiently for institution that Lu teaches this portion of the claim. 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, on this record, by Patent Owner's arguments that the combination of Lu and Illumina fails to teach the limitations of claim 1. Prelim. Resp. 28–35. Patent Owner argues that the inventors of the '350 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). The combination of Lu and Illumina, Patent Owner argues, "does not identify cancer drugs independent of cancer types." *See* Prelim. Resp. 28–35.

At this stage of the proceeding, 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. Ex. 1001, 14:1–5; *see also id.* at 16:64–17:27. 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 EGFR, KIT, TOP1, MLH1, PTEN, PDGFRA and ESR1. *Id.* at 17:3–4. 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 all these molecular targets were known in the art to be associated with cancer. *See* Ex. 1004

¶ 22; Ex. 1005, 4 (Table 1); Ex. 1002 ¶¶ 86–88. Claim 1 also recites "a listing of available therapeutic agents for" these molecular targets, which, according to the '350 patent, are therapeutic agents known to interact with the molecular targets. Ex. 1001, 4:13–21, 17:8–9. 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 16:64–65; *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.

On this record and at this stage of the proceeding, therefore, we are satisfied that Petitioner establishes sufficiently for institution that the combination of Lu and Illumina satisfies the limitations of claim 1.

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).

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. 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. 48–49; *see* Ex. 1002 ¶¶ 113–114; 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. 49–50; *see* Ex. 1002 ¶¶ 114–115, 147; 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. 51–58; Ex. 1002 ¶ 120. 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 ¶ 120; *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. 54–58; *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).

3. *Summary*

In summary, based on the record before us and the application of the reasonable likelihood standard, we are satisfied that Petitioner has shown sufficiently for instituting trial that it would prevail in showing claim 1 unpatentable for obviousness over Lu in view of Illumina. Claims 2–14 depend on claim 1. We have reviewed Petitioner's arguments and supporting evidence as to these claims, and find them sufficient for institution based on the current record. *See* Pet. 38–58. We also note that Patent Owner does not raise additional arguments specific to the dependent claims at this stage of the proceeding. *See generally* Prelim. Resp. Thus, in light of *SAS* and USPTO Guidance, we also institute an *inter partes* review of dependent claims 2–14 on the same ground.

F. *Asserted Ground of Unpatentability Based on Lu in View of Illumina and Muraca*

Petitioner contends that claims 2 and 3 are also unpatentable as obvious over Lu, Illumina, and Muraca. Pet. 58–64. Claims 2 and 3 relate to a user's entry of certain information remotely or over an Internet connection. Ex. 1001, 17:28–33. We have reviewed Petitioner's arguments and evidence as to these claims, and determine that the information presented establishes a reasonable likelihood that Petitioner would also prevail in showing that those claims are unpatentable under 35 U.S.C.

§ 103(a). See Pet. 58–64. In particular, Muraca teaches a molecular profiling system where users "at different physical locations" "can both access and add . . . information" to a database by accessing an Internet webpage. See Ex. 1006 ¶¶ 18, 19, 34, 125, 151, 188, 190. At this stage of the proceeding, Patent Owner challenges this ground by referencing the arguments it made with respect to the alleged combination of Lu and Illumina. Prelim. Resp. 35. Again, we are not persuaded by these arguments for the reasons discussed above. See supra § III.E.

G. *Asserted Ground of Unpatentability Based on Lu in View of Illumina and McDoniels-Silvers*

Finally, Petitioner contends that claims 7, 11, and 12 are unpatentable as obvious over Lu, Illumina, and McDoniels-Silvers. Pet. 64–68. These claims specify that the patient has received drug therapy for cancer (claim 7), and has failed to respond to that therapy (claims 11 and 12). Ex. 1001, 18:7–9, 18–22. We have reviewed Petitioner's arguments and evidence as to these claims, and determine that the information presented establishes a reasonable likelihood that Petitioner would also prevail in showing that those claims are unpatentable under 35 U.S.C. § 103(a). *See* Pet. 64–68. In particular, McDoniels-Silvers discloses the use of a cDNA human expression microarray to screen clinical samples from patients with prior cancers, including a patient who had been treated with radiation and a patient who underwent multiple rounds of chemotherapy. See Ex. 1007, Table 1. At this stage of the proceeding, Patent Owner challenges this ground by referencing the arguments it made with respect to the alleged combination of Lu and Illumina. Prelim. Resp. 35. Again, we are not

persuaded by these arguments for the reasons discussed above. *See supra* § III.E.

IV. CONCLUSION

After considering the evidence and arguments presented in the Petition, Preliminary Response, Reply, and Sur-Reply, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least one claim of the '350 patent is unpatentable. Thus, in accordance with USPTO Guidance and *SAS*, we institute an *inter partes* review of all of the challenged claims on all grounds set forth in the Petition. Our determinations at this stage of the proceeding are based on the evidentiary record currently before us. This decision to institute trial is not a final decision as to patentability of any claim for which *inter partes* review has been instituted. Any final decision will be based on the full record developed during trial.

V. ORDER

Accordingly, it is:

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–14 of U.S. Patent No. 8,880,350 B2 is instituted with respect to all grounds set forth 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 commencing on the entry date of this Decision.

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