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Paper No. 7
Date: 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 IPR2019-00165
Patent 9,092,392 B2

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

SAWERT, *Administrative Patent Judge.*

DECISION
Denying 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 1–20 of U.S. Patent No. 9,092,392 B2 (Ex. 1001, "the '392 patent"). Caris MPI, Inc. ("Patent Owner") did not file a Preliminary Response.

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).

Applying those standards, and upon consideration of the information presented in the Petition, we determine that Petitioner has not demonstrated a reasonable likelihood of success in proving that at least one claim of the '392 patent is unpatentable. Accordingly, we do not institute an *inter partes* review of any claim of the '392 patent.

II. BACKGROUND

A. *Related Proceedings*

The '392 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: IPR2019-00164 (U.S. Patent No. 8,880,350 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

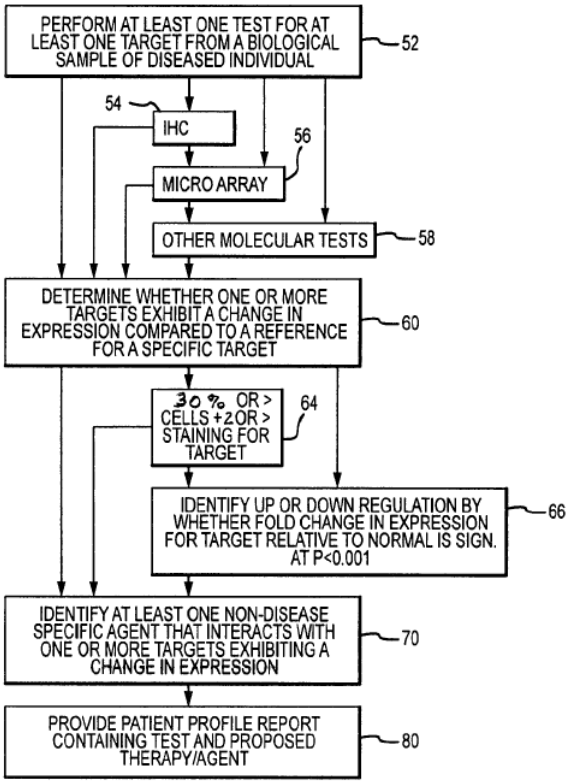
B2). Trials were instituted in IPR2019-00166 and IPR2019-00203 on May 14, 2019. *See* IPR2019-00166 (Paper 12); IPR2019-00203 (Paper 12).

B. *The '392 patent*

The '392 patent, titled "Molecular Profiling of Tumors," issued on July 28, 2015. Ex. 1001, (54), (45). The '392 patent relates to "methods and systems of molecular profiling of diseases, such as cancer." *Id.* at (57) (Abstract). The '392 patent states that, "[i]n some embodiments, the molecular profiling can be used to identify treatments for a disease, such as treatments . . . not initially identified as a treatment for the disease or not expected to be a treatment for a particular disease." *Id.*

According to the '392 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 1:35–39. The '392 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 1:51–55. Thus, the '392 patent states, there is a need to measure "a larger number of targets" or "molecular mechanisms, genes, gene expressed proteins and/or combinations of such," to "find additional targets or molecular findings that can be exploited by using specific therapeutic agents." *Id.* at 2:11–16. The '392 patent states that this approach would provide patients "with a viable therapeutic alternative to those treatment regimens which currently exist." *Id.* at 2:18–20.

Figure 2 of the ’392 patent, reproduced below, provides an overview of an exemplary “method for determining individualized medical intervention” that utilizes a patient’s molecular profile. *Id.* at 7:33–36.



In step 52, at least one test is performed for at least one molecular target (e.g., one or more genes, proteins, molecular mechanisms, and/or combinations thereof) from a patient’s biological sample. *Id.* at 144:25–34. Tests that may be performed include an immunohistochemistry (IHC) analysis 54, a microarray analysis 56, and/or any other known molecular tests 58. *Id.* at 145:4–6.

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 145:16–19. 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 145:19–39.

Next, "at least one non-disease specific agent is identified that interacts with each target having a changed expression in step 70." *Id.* at 145:40–43. The '392 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 145:44–48. 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 145:63–65.

The '392 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. *See id.* at 136:49–144:18. The internal databases can include information about the patient biological sample, patient test results from molecular profiling, clinical data, and study protocols. *Id.* at 144:10–14. The external databases can include drug libraries, gene libraries, disease libraries, and public databases such as GenBank. *Id.* at 144:14–18. The computerized system identifies a candidate treatment for a disease by comparing a patient's molecular profile to a database that maps treatments and molecular profiling results. *See id.* at 51:11–44. The '392 patent teaches that the maps may be created, for example, by reviewing literature for links between biological agents and therapeutic agents. *Id.* at 51:23–25.

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 a therapeutic agent for an individual with colorectal cancer comprising:
>
> a. at least one nucleic acid sequencing device configured to assay a plurality of molecular targets in a biological sample from the individual with colorectal cancer to determine molecular profile test values for the plurality of molecular targets, wherein the plurality of molecular targets comprises BRAF, PIK3CA, EGFR and PTEN;
>
> 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 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 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) along and the at least one therapeutic agent identified in (d).

Id. at 164:37–67.

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 '392 patent:

1. Daniel D. Von Hoff and Robert Penny, U.S. Patent Application Publication No. 2008/0014146 A1 (Jan. 17, 2008) (Ex. 1074) ("Von Hoff");

2. Tobias Sjöblom et al., *The Consensus Coding Sequences of Human Breast and Colorectal Cancers*, 314 SCIENCE 268–74 (Oct. 13, 2006) ("Sjöblom," Ex. 1087); and

3. Alberto Bardelli and Victor E. Velculescu, *Mutational analysis of gene families in human cancers*, CURRENT OP. IN GENETICS & DEV. (2005) ("Bardelli," Ex. 1075).

E. *Asserted Ground of Unpatentability*

Petitioner challenges the patentability of the '392 patent's claims on the following ground:

Reference(s)	Basis	Claim(s) challenged
Von Hoff, Sjöblom, and Bardelli	§ 103(a)	1–20

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

III. ANALYSIS

We organize our analysis into five sections. First, we address the priority date for the '392 patent. Second, we address the level of ordinary skill in the art. Third, we address claim construction. Fourth, we provide an

overview of the asserted references. And fifth, 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. *Priority Date*

The '392 patent is a continuation of Application No. 12/658,770, filed February 12, 2010, which in turn is a continuation-in-part of two applications: Application No. 11/750,721, filed on May 18, 2007, and Application No. 13/188,350, which traces back to an application filed on October 14, 2009. Ex. 1001, (63). The '392 patent also claims priority to several provisional applications, the earliest of which was filed on May 18, 2006. *Id.* at (60). Among these priority applications, Petitioner contends that the first possible support for "PIK3CA" and "BRAF," molecular targets recited in claim 1, is found in Provisional Application No. 61,217,289 ("the '289 provisional application"), filed on May 28, 2009. Pet. 17–18 (citing Ex. 1084, 18[1]; Ex. 1002 ¶¶ 106–107).

Based on the record at this stage of the proceeding, we determine that Petitioner has made a sufficient showing that the claims of the '392 patent are not entitled to a priority date earlier than May 28, 2009. BRAF appears to be first listed in the '289 provisional application in a listing of five genes "that are examined for alterations" in their DNA sequences. *See* Ex. 1084, 17–18. PIK3CA also appears to be first mentioned in the '289 application in the title of a scientific publication. *See* Ex. 1084, 52; *see also* Ex. 1002 ¶¶ 107–108.

[1] For this Exhibit, the page numbers refer to the pagination added by Petitioner.

Patent Owner has the burden of producing evidence in support of any contention that the challenged claims are entitled to an earlier filing date. S*ee Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008) (holding that patent owner has the "burden of going forward with evidence either that the prior art does not actually anticipate, or, as was attempted in this case, that it is not prior art because the asserted claim is entitled to the benefit of a filing date prior to the alleged prior art").

B. *Level of Ordinary Skill in the Art*

We consider the asserted grounds of unpatentability in view of the understanding of a person of ordinary skill in the art. Petitioner contends, and Dr. Spellman testifies, that as of the earliest priority date for the '392 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. 15–16 (citing Ex. 1002 ¶ 31).

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 from the perspective of an ordinary artisan at the time of the invention. *See* Ex. 1002 ¶¶ 4–15.

C. *Claim Interpretation*

Based on the filing date of the Petition (November 6, 2018), the Board interprets claim terms in the '392 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).[2]

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. 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

[2] 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. 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) (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*.

are in controversy, and only to the extent necessary to resolve the controversy.").

D. *Asserted References*

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

1. *Van Hoff*

Von Hoff is a U.S. patent application published January 17, 2008. Ex. 1074, (43). Von Hoff is listed as an inventor of the '392 patent. Ex. 1001, (72). Petitioner acknowledges that the '392 patent is a continuation-in-part of U.S. Application No. 11/750,721, filed on May 18, 2007, which published as the Von Hoff reference. Pet. 19. Petitioner argues that Von Hoff nonetheless qualifies as prior art under 35 U.S.C. § 102(b) because, as discussed above, the claims of the '392 patent are not entitled to a priority date earlier than May 28, 2009. *Id*. at 19–20. Petitioner also contends that Von Hoff lists only two inventors of the '392 patent and thus is prior art by "another" under § 102(a). *Id.* at 20 (citing Ex. 1002 ¶ 114).

Von Hoff describes a system and method for determining individualized medical intervention for a particular disease state. Ex. 1074 ¶ 8. Figure 2 of Von Hoff is identical to Figure 2 of the '392 patent, reproduced above. *See* § II.B; *see also* Ex. 1074 ¶ 17 (describing Figure 2 as a flowchart of "a method for determining individualized medical intervention for a particular disease state that utilizes molecular profiling of a patient's biological specimen that is non disease specific").

Von Hoff discloses performing at least one test for at least one target from a biological sample of a patient (i.e., step 52 in Figure 2). *Id.* ¶ 53.

The target may be one or more genes, one or more gene expressed proteins, one or more molecular mechanisms, and/or combinations thereof. *Id.* Von Hoff teaches that the test can include IHC analysis, micro array analysis, and other molecular tests. *Id.* The gene can be, among others, PTEN and KIT, and the gene expressed protein can be, among others, c-kit. *Id.* ¶¶ 9–10.

Von Hoff's method further includes determining whether one or more targets exhibit a change in expression compared to a normal reference for the particular target (i.e., step 60 in Fig. 2). *Id.* ¶ 55. Subsequently, a non-disease specific agent that interacts with each target having a changed expression is identified (i.e., step 70 in Fig. 2). *Id.* ¶ 56, Table 1. The agent may be a therapeutic drug or compound capable of interacting with the sample target that has exhibited a change in expression. *Id.* Von Hoff discloses that identification of the drug therapy may be conducted via an automated review of an extensive literature database and/or database generated from clinical trials. *Id.* ¶¶ 8, 52. Such a database may have stored data, such as patient data, biological sample data, prior treatment and protocol data, patient clinical data, molecular profiling data of biological samples, data on therapeutic drug agents and/or investigative drugs, a gene library, a disease library, a drug library, and other types of data stored within the database. *Id.* ¶¶ 24, 59.

Von Hoff further teaches that a patient profile report can be provided that includes test results for various targets and any proposed therapies based on the results (i.e., step 80 in Fig. 2). *Id.* ¶ 57.

2. *Sjöblom*

Sjöblom presents the study of a systemic analysis of genetic alterations in human breast and colorectal cancers. Ex. 1087, Abstract. The

study was performed to "provide clues to the cellular processes underlying tumorigenesis" and "for diagnostic and therapeutic purposes." *Id.* at 268. Sjöblom states that the "determination of the human genome sequence and recent improvements in sequencing and bioinformatic approaches" make possible the examination of the cancer cell genome "in a comprehensive and unbiased manner." *Id.*

Sjöblom chose breast and colorectal cancers for study because, together, they account for about 20% of the total cancer diagnoses each year. *Id.* Sjöblom also "focused on a set of protein-coding genes, termed the consensus coding sequences (CCDS), that represent the most highly curated gene set" then available. *Id.* Using PCR amplification and sequencing, Sjöblom analyzed the sequences of 13,023 genes in 11 cell lines or xenografts of each cancer type. *Id.* Sjöblom compared those sequences to normal sequences to identify subsets of "bona fide" somatic mutations. *Id.* at 268–69.

Specifically, of the 13,023 genes evaluated, Sjöblom found that 1,149 had mutation(s), 236 were "validated" (i.e., not screened out due to, e.g., silent mutations, false positives, PCR or sequencing artifacts), and 189 of those were "candidate cancer genes" ("*CAN* genes")—122 in breast cancers, and 69 in colorectal cancers. *Id.* at 269–70. Sjöblom describes *CAN* genes as those genes "most likely to have been subjected to mutational selection during tumorigenesis." *Id.* at 270. The *CAN* genes for breast and colorectal are listed in tables S5 (Ex. 1093) and S6 (Ex. 1094), respectively.

Sjöblom concludes that, "[f]or diagnostics, the *CAN* genes define a relatively small subset of genes that could prove useful as markers for neoplasia," and further that, "some of these genes, particularly those on the

cell surface or those with enzymatic activity, may prove to be good targets for therapeutic development." *Id.* at 274.

3. *Bardelli*

Bardelli provides a review discussing "the findings and concepts that have emerged from the recent mutational analyses of the colorectal cancer genome" performed by various research groups. Ex. 1075, 5. Bardelli states that the human genome contains over 20,000 genes. *Id.* "The availability of a reference human genome sequence coupled with advances in high-throughput DNA analysis," however, "has opened up new strategies for cancer gene identification." *Id.* at 6. Bardelli states that recent mutational analyses have focused on gene families involved in signal transduction, such as kinases and phosphatases. *Id.* at 5. Bardelli states that the gene PI3KCA has been identified "as one of the most commonly mutated oncogenes in human cancer." *Id.*

E. *Asserted Ground of Unpatentability Based on Van Hoff in View of Sjöblom and Bardelli*

Petitioner contends that claims 1–20 are unpatentable as obvious over Van Hoff, Sjöblom, and Bardelli. Pet. 26–58. 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).

Petitioner contends that the combination of Van Hoff, Sjöblom, and Bardelli teaches or suggests each limitation of claims 1–20. *Id.* at 26–52; *see also* Ex. 1002 ¶ 197 (claim chart). For example, as to claim 1, Petitioner contends that Van Hoff discloses each limitation of that claim, but does not explicitly teach "at least one nucleic acid sequence device, "colorectal cancer," and the specific molecular targets BRAF and PIK3CA. *Id.* at 26–38, 52–53. Petitioner relies on Sjöblom for teaching "the use of a nucleic acid sequencing device that assayed thousands of genes from colorectal tumor samples to obtain molecular profile test values for colorectal cancer." *Id.* at 28 (citing Ex. 1002 ¶ 150). Petitioner also relies on Sjöblom for sequencing the genes BRAF, PIK3CD, EGFR, and PTEN. *Id.* at 30 (citing Ex. 1089, 8 (PIK3CD), 551 (BRAF), 518–519 (EGFR), 892 (PTEN[3]); Ex. 1002 ¶ 152). Petitioner relies on Bardelli for teaching "PI3KCA as one of the most commonly mutated oncogenes in human cancer." *Id.* (citing Ex. 1075, Abstract).

Petitioner also contends that an ordinarily skilled artisan would have had a reason to combine the teachings of Van Hoff, Sjöblom, and Bardelli, with a reasonable expectation of success, based on the teachings of the art, including the teachings of these references themselves. Pet. 52–59. As to the teachings of the art, Petitioner contends that, before May 18, 2009, "it was a common goal of many researchers in the field of personalized medicine to obtain comprehensive genetic or molecular profiles of

[3] According to Dr. Spellman, PTEN is also known in the art as TEP1, as referred to by Sjöblom. Ex. 1002 ¶ 129.

individuals to provide more effective diagnostic and therapeutic options" to patients. Pet. 53–54 (citing Ex. 1002 ¶ 135; Ex. 1050, 27–28). Petitioner also contends that an ordinarily skilled artisan would have been aware of multiple techniques for obtaining molecular profile information, the use of bioinformatics for leveraging available biomarker data, as well as multiple databases tying therapies to genetic markers. Pet. 54–56 (citing Ex. 1002 ¶¶ 135–139; Ex. 1074, Abstract; Ex. 1087, Abstract; Ex. 1075, Abstract; Ex. 1050, 30–31; Ex. 1051, 170–171, 173). Petitioner contends that, in view of these teachings, an ordinarily skilled artisan "would have been motivated to combine Von Hoff, Sjöblom and Bardelli to obtain molecular profile information for a patient with colorectal cancer and to compare that information with publicly-available data regarding available therapeutics to attempt to match the patient to a suitable treatment based on her molecular profile." *Id.* at 56 (citing Ex. 1002 ¶¶ 135–139).

As to the specific teachings of the references relied upon for this challenge, Petitioner contends that (1) Sjöblom provides explicit motivation to go beyond the SNP-microarray profiling disclosed in Van Hoff and to obtain more comprehensive sequence profiles of cancers using large-scale sequencing, *id.* at 57 (citing Ex. 1074 ¶ 53; Ex. 1071, 3521; Ex. 1087, 268; Ex. 1002 ¶ 141); (2) Van Hoff suggests screening "a larger number of targets that can be exploited by using specific therapeutic agents," and that "Sjöblom explicitly teaches a 'systemic analysis' of genetic alterations in cancer," to find "new targets for diagnostic and therapeutic intervention," *id.* at 57–58 (citing Ex. 1074 ¶ 6; Ex. 1002 ¶ 142–143; Ex. 1087, Abstract, 273); and (3) "Sjöblom further provides the explicit motivation to combine the teachings of Bardelli because it cites Bardelli when describing prior

selection of genes for mutation analyses in cancer," *id.* at 58 (citing Ex. 1087, 268, 274; Ex. 1002 ¶ 144; Ex. 1075, Abstract).

Having reviewed the record, we determine that Petitioner has not shown sufficiently for institution that an ordinarily skilled artisan would have had a reason to combine the prior art to obtain the claimed system wherein the molecular targets comprise BRAF, PIK3CA, EGFR, and PTEN. 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).

The Petition fails because Petitioner has not explained adequately for institution why an ordinarily skilled artisan would have had a reason to sequence all 13,000+ genes disclosed in Sjöblom to identify a therapeutic agent for an individual with colorectal cancer. We begin by emphasizing that "obviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention." *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015). Although the record generally supports Petitioner's contention that the prior art in general, and Sjöblom specifically, provides a reason to obtain molecular profile information for a patient with colorectal cancer by sequencing, Pet. 56–57,

the record does not adequately support Petitioner's contention that an ordinarily skilled artisan would have had a reason to obtain that information by sequencing all 13,000+ genes disclosed in Sjöblom, in view of Sjöblom's express teaching that less than 1% of those genes are implicated in colorectal cancers. Put differently, the mere possibility that an ordinarily skilled artisan could have sequenced more than half of an individual's known genes[4] does not necessarily mean that the artisan would have been motivated to do so. *See Pers. Web Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 993–94 (Fed. Cir. 2017) (stating that "reasoning [that] seems to say no more than that a skilled artisan, once presented with the two references, would have understood that they could be combined" "is not enough," because "it does not imply a motivation to pick out those two references and combine them to arrive at the claimed invention").

In particular, Petitioner does not explain sufficiently for institution why an ordinarily skilled artisan would have undertaken large-scale sequencing for an individual when Sjöblom teaches that, out of the 13,023 genes sequenced, only 236 genes had "validated" mutations, and out of those genes, only 69 were identified as *CAN* (i.e., cancer candidate) genes in colorectal cancers. Ex. 1087, 269–70. Petitioner does not discuss or mention the *CAN* genes in its analysis, presumably because none of the *CAN* genes that Sjöblom identifies for colorectal cancer include the molecular targets recited in claim 1: BRAF, PIK3CA, EGFR, and PTEN. *See* Ex. 1094 (listing the 69 colorectal *CAN* genes). Thus, it is not clear on this record why the skilled artisan would have been prompted to sequence

[4] According to Bardelli, the human genome contains over 20,000 genes. Ex. 1075, 5.

13,000+ genes, when Sjöblom points specifically to the *CAN* genes as "most likely to have been subjected to mutational selection during tumorigenesis." Ex. 1087, 270.

Petitioner's failure to acknowledge Sjöblom's teaching of the colorectal *CAN* genes is particularly troubling in this case because Petitioner takes Sjöblom's teachings as to those genes out of context to support its rationale for combining the prior art. Specifically, Petitioner contends that Sjöblom teaches "some of the identified genes, 'particularly those on the cell surface or those with enzymatic activity, may prove to be good targets for therapeutic development.'" *See* Pet. 58 (quoting Ex. 1087, 273); Ex. 1002 ¶ 143. But the full quotation from Sjöblom makes clear that the "good targets for therapeutic development" are only a subset of the *CAN* genes, rather than the originally sequenced 13,000+ genes:

> For diagnostics, *the CAN genes* define a relatively small subset of genes that could prove useful as markers for neoplasia. Finally, *some of these genes*, particularly those on the cell surface or those with enzymatic activity, may prove to be good targets for therapeutic development.

Ex. 1087, 274 (emphases added). Given Sjöblom's express teaching that only *some of the CAN genes* may be good targets for therapeutic development, it is not clear on this record why an ordinarily skilled artisan would have taken the path Petitioner alleges, i.e., performing large-scale sequencing of 13,023 genes for an individual.

Petitioner does not persuade us sufficiently for institution that "a POSA would not have felt arbitrarily limited in capacity to select only a handful of [molecular] targets to assay." Pet. 59. Petitioner relies on Dr. Spellman's Declaration for support, but Dr. Spellman's testimony on this

issue is conclusory and ignores certain teachings of Sjöblom. Specifically, Dr. Spellman states that each prior-art reference "us[es] technologies capable of interrogating a very large plurality of genes," thus implying that sequencing 13,000+ genes to identify therapeutic agents for an individual would have been routine in the art. Ex. 1002 ¶ 145. But neither Petitioner nor Dr. Spellman provide evidence that such high-throughput DNA sequencing was, in fact, routine as of May, 2009. See 37 C.F.R. § 42.65(a) (opinion testimony that does not disclose underlying facts "is entitled to little or no weight").

Dr. Spellman also does not attempt to explain how an ordinarily skilled artisan would have navigated the many technical challenges Sjöblom identifies: the "major technical challenge" of "discerning somatic mutations from the large number of sequence alterations," *see* Ex. 1087, 273 (finding that only 0.23% of the 557,029 nonsynonymous sequence alterations detected in the discovery screen were "legitimate somatic mutations"); the high error rate associated with newly-developed sequencing methods, *id.*; the need for "careful design of primers . . . to eliminate sequence artifacts due to the inadvertent amplification and sequencing of related genes," *id.*; and "the inherent difficulties in determining the consequences of somatic mutations, even those that alter the amino acid sequence of highly annotated and well-studied genes," *id.*

Although we understand that an ordinarily skilled artisan is a person of ordinary creativity, not an automaton, "[w]ithout any explanation as to how or why the references would be combined to arrive at the claimed invention, we are left with only hindsight bias that *KSR* warns against." *Metalcraft of Mayville, Inc. v. The Toro Co.*, 848 F.3d, 1358, 1367 (Fed. Cir.

2017). Thus, under the particular facts of this case, we are not persuaded that Petitioner has established sufficiently for institution a reason to combine Von Hoff, Sjöblom, and Bardelli.

IV. CONCLUSION

After considering the evidence and arguments presented in the Petition, we determine that Petitioner has not demonstrated a reasonable likelihood of success in proving that at least one claim of the '392 patent is unpatentable. Accordingly, the Petition is *denied*, and no trial is instituted.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *denied*, and no trial is instituted.

PETITIONER:

David Cavanaugh
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